THE PRINCIPLES AND PRACTICE OF TROPICAL MEDICINE

PART TWO

PREFACE

The first part of Dr Napier's *Principles and Practice of Tropical Medicine* was published in 1943 when hope was expressed that the second part would be ready within a year. But that hope could not be fulfilled owing to unforeseen circumstances. The author had already left India for the United States and the manuscript was not received until 1944. Difficulties arose firstly from labour troubles in the press and then from communal disturbances which caused serious dislocation of all business in the city for a fairly long time. Meanwhile Dr John Lowe who was entrusted with seeing the volume through the press went home on leave leaving it to me to complete the task. The index covering both volumes had still to be compiled and this was done as expeditiously as possible. The delay in publication has no doubt caused some inconvenience to those who already have the first part and is very much regretted.

School of Tropical Medicine
Calcutta October 1947

YAWS AND ASSOCIATED DISEASES

PINTA

BEJEL

Introduction.—There are at least three tropical syndromes caused by spirochætes morphologically indistinguishable from the parasite of syphilis that have been given the status of named diseases they are yaws, pinta and bejel. All three are looked upon as modified forms of syphilis by some workers and as distinct diseases by others They have many common features but perhaps the most important is that they are all three non venereal in origin.

There are probably other allied, similar or identical diseases in other primitive and isolated populations An example of such a condition is *irkintja* of Central Australia recently described by Hackett (1936) who believes that the condition is identical with, or at least closely related to yaws. In this condition there are early lesions similar to those of yaws usually in childhood and later gangosa boomerang leg, and keloid scarring

YAWS or FRAMBŒSIA

Definition.—Yaws or framboesia (French *framboise* = raspberry) known as *pian* in the French colonies and by many other local names elsewhere, is a contagious disease resembling syphilis but non venereal in origin, occurring mainly amongst aboriginal populations in the tropics characterized in its florid stage by multiple granulomatous lesions of the

skin and later by a variety of lesions of the skin subcutaneous tissues and bones it is caused by a spirochætal organism *Treponema pertenue* that is readily recoverable from the cutaneous lesions.

Historical —It is not possible to identify definitely as yaws any of the skin diseases that are mentioned in ancient writings, though several would pass as this disease

In the records of the fifteenth and sixteenth centuries, the disease is obviously confused with syphilis a confusion that still exists even to-day Bontius appears to have recognized the disease in the East Indies, and early in the eighteenth century it was described as occurring amongst African slaves in North America. Yaws was well established as a distinct disease entity in medical literature by the end of the eighteenth century

EPIDEMIOLOGY

Geographical distribution —It has a wide tropical distribution and all the more important endemic centres are within the true tropics. It occurs in Central and South America, in the West Indies extensively in equatorial Africa including the Sudan and Abyssinia in India Burma Ceylon, Indo-China, Malaya and the East Indies generally and in Northern and Central Australia and certain Pacific islands The most important subtropical endemic foci are in Algiers and Tripoli in North Africa in Assam in India, and in northern Burma.

In India it is much more widespread than is generally supposed occurring in Cochin, Travancore, Hyderabad, the Central Provinces, Chota Nagpur Bihar, Orissa, Santhal Parganas Chittagong Hill Tracts Manipur Cachar and several other places in Assam Nowhere however has it assumed seriou epidemic proportions and spread to the general populations of the plains of India.

It is said to be increasing in East Africa particularly in Kenya Tanganyika and Uganda and to be decreasing in Ceylon in Barbados and in the Guianas but as it is a disease that spreads rapidly and produces *a high degree of immunity it is likely that it will appear in epidemic* waves in countries where conditions are particularly suitable for its spread and die down or disappear when all susceptible persons (i.e the children born since the last epidemic wave and the few adults who previously escaped infection) have been infected.

Epidemic features —It is a disease of rural districts rather than towns

The incidence of the disease varies considerably In certain isolated islands and other primitive populations practically every individual becomes infected sooner or later and usually sooner that is in childhood In some tropical countries in equatorial Africa for example the disease is a very serious public health problem (*e g* over 300,000 persons were treated within a few years in the Belgian Congo which has a population of only about 10,000,000 and in the coastal region of Columbia it is estimated that there are 80,000 cases) whereas in India although yaws occurs in many parts of the country it is seldom a serious problem and the number of cases treated annually will only amount to a few hundred at a generous estimate.

The tropical distribution suggests that temperature is an important factor Experience has shown that when a case is imported into a temperate country the infection does not spread It has been found in India that the hill folk who tend to get the disease when they come down to the foothills or into the hot humid plains do not take the disease back to their own villages if these are situated at any great height.

Humidity is also important and most of the endemic countries enjoy a high degree of humidity for a considerable part of the year and luxuriant

vegetation, however the disease also occurs in Algeria and Tripoli which are relatively dry countries as well as being outside the tropics

Racial distribution—In its natural form it is a disease that is confined almost entirely to primitive peoples. This is most strikingly demonstrated in India where it occurs amongst primitive hill folk, but seldom spreads to any extent amongst the plains population (*vide supra*) This is almost certainly not due to personal susceptibility or immunity as the disease is easily transmitted experimentally to individuals of any racial type, but probably to the habits of the people who have a low standard of personal cleanliness and live and sleep in primitive huts closely huddled together

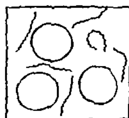
Age and sex distribution—The disease is most common in children up to the age of 15 years, though it is uncommon in infants under six months, but adults who have escaped infection in their childhood also suffer from it, mothers frequently contracting the infection from their children. In highly endemic areas, children usually contribute at least 90 per cent of the cases but in isolated communities where the infection is reintroduced at longer intervals a large proportion of adults will become infected. All contagious infections tend to spread more rapidly amongst children on account of their habits but the most important influence in these cases is undoubtedly the immunity acquired by adults during previous outbreaks.

Most writers report that males are more commonly infected than females. This is probably due to the greater freedom allowed to male children. Chambers (1938) points out that in Jamaica the only age groups in which females predominate is from 20 to 29 years, this is an age at which women would be most closely associated with infants and children and would be likely to be infected from them.

ÆTIOLOGY

Historical.—Castellani in 1905 first isolated from yaws lesions an organism indistinguishable from the organism of syphilis, and named it *Spirochæta pertenue* both these organisms were later placed in the genus, *Treponema*

The causal organism.—*Treponema pertenue* is a very slender (0.25 microns) spirochætal organism from 8 to 18 microns in length it has from five to a dozen regular spirals 1 to 1 5 microns deep at intervals of about 1 micron which tend to taper towards each end where there may be a single flagellum-like filament. It is flexible and moves by spiral rotation. It is morphologically identical with *Treponema pallidum* the causal organism of syphilis


Figure 139 *Treponema pertenue*

Culture and animal inoculation—Culture of this organism was claimed by Noguchi and later by Hata, the former grew it in ascitic fluid to which kidney tissue had been added anaerobically Most other workers have failed to satisfy themselves that they have produced a true culture and at any rate the procedure is not a practical diagnostic method

Successful inoculation has been produced in man, higher apes, monkeys, and rabbits in the two latter animals only local lesions are produced.

Distribution in the tissues.—The spirochæte is found in the primary and secondary skin lesions, in the spleen, and in the bone marrow their presence in the blood has been demonstrated by inoculation.

Transmission.—This takes place by means of direct contact, the organism from the exudate of a lesion entering the new host through an

abrasion although possibly an invisible abrasion in his skin Whenever the point has been carefully investigated a history of close contact with some person with florid lesions has been obtained in almost every case and, when mothers are infected by their infants the common sites of the primary lesion are on the breast at the bend of the elbow or on the hip places where direct contact most commonly occurs

The mechanical transfer of infection by means of flies is considered to be a possible alternative method in some places and the small fly, *Hippelates pallipes* has been experimentally incriminated as a mechanical transmitter in Jamaica Certain species of *Musca* have also been shown to be potential mechanical carriers of viable spirochætes but a biological cycle in any insect has never been seriously suggested.

Man is the only known reservoir of infection

Congenital transmission never occurs

The relation of the causal organism of yaws to that of syphilis—This is a problem on which much work has been done during the last four decades without any final conclusion yet being reached

Morphologically the organisms are identical culturally no definite differences have been established serologically in the antigenic structure of the organisms common elements but also distinct differences have been shown to exist in animals readily distinguishable lesions are produced by these two organisms and in man there are marked differences in the two diseases they cause.

Whether syphilis is a specialized form of yaws that has in the course of years undergone some change through being transmitted venereally amongst people of civilized races whether yaws is a mild form of syphilis that has lost some of its characteristics through frequent non venereal passage amongst primitive people for example possibly as a result of their heavy malarial infection or whether which seems to the writer most likely they both arose from a common ancestor probably in prehistoric times and each developed in its own way are matters of little more than academic interest. Except in the crude test of morphology, the differences are far greater than those frequently observed between different strains of the same organism and the general opinion is that *Treponema pallidum* and *Treponema pertenue* are closely related but of quite distinct species

Immunology—Immunity to superinfection is not immediate and complete but it appears to take several months or even years to develop and if early treatment is given reinfection becomes possible. Many cases of syphilis have been reported in individuals who have or have had yaws and conversely yaws has developed in syphilitics but there appears to be little doubt that populations that have been heavily infected with yaws enjoy some degree of immunity from syphilis. The reverse is probably true but not so easily demonstrated unless one takes the view that the relative immunity to yaws of towns-folk in countries where yaws is common in the rural districts is due to the heavy syphilization of the town-dwellers but this argument cannot be universally applied

Animal experiments indicate that infection with syphilis gives complete protection against yaws but that yaws infection only gives partial protection against syphilis

The Wassermann and Kahn reactions become positive three to four weeks after the appearance of the primary lesions and are constantly positive after about the eighth week they remain positive for several years or as long as the infection is active. Those affected with yaws in early childhood usually lose their positive serum reactions after puberty so that whenever positive results are obtained in such persons they may usually be taken as evidence of a superimposed syphilitic infection.

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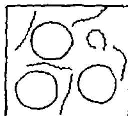


Figure 139. *Treponema pertenue.*

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PATHOLOGY

The spirochæte gains entry through an abrasion, or possibly even through the unbroken skin and enters the deeper layers of the epidermis where it multiplies producing a cellular (polymorphonuclear and plasma cell) reaction and œdema The proliferation of the cells of the malpighian layer causes both a downgrowth of the interpapillary processes and also a general upward growth that pushes up and eventually splits the stratum corneum into lamellæ between which fibrinous coagula form. There is also increased vascularity plasma cell and lymphocyte infiltration and some proliferation of the reticular cells of the papillæ. The spirochætal infection is mainly confined to the epidermis but eventually spreads to the surrounding lymph channels in the dermis and finally reaches the blood when generalization of the infection occurs.

From the moment of entry of the spirochæte, the lesion of this first stage takes three to four weeks to develop and after generalization has taken place, there is usually an interval of two to three months before the secondary lesions appear these are multiple and appear on many parts of the body surface The typical secondary yaws lesion is similar to the primary lesion described above.

After a much longer interval up to several years a third group of lesions may appear typically they are *gummatous inflammatory lesions* of the subcutaneous and other tissues that may lead to gummatous ulceration of the skin, to fibrotic tumours in the skin or subcutaneous tissues especially around the joints to gumma and rarefaction of the bones and/or to diffuse keloid like formations of the skin

It is suggested that the tertiary lesions are of the nature of an allergic reaction.

Some writers describe tertiary lesions of the viscera and the arteries similar to those of syphilis, but the authenticity of such lesions seems doubtful, and most observers agree that the lesions of yaws are mainly epiblastic that is to say affecting the skin and bones in contrast to syphilis in which the causal organism is panblastotropic that is it affects the tissues of all three embryonic layers.

The lesions that occur can thus be placed in three groups the primary or initial lesions (mother yaw ') the secondary or lesions of the generalized stage, and the tertiary lesions or sequelæ Between these three stages and the three stages of syphilis, there is in the writer's opinion sufficient similarity to justify the adoption of the terms primary secondary and tertiary stage but there is not exact parallelism and for this reason some writers avoid these terms

SYMPTOMATOLOGY

The clinical picture corresponding to these three pathological stages will be considered under three separate headings —

The primary stage.—There is usually a single lesion but it is possible for there to be more than one, if infection occurs at two places After an incubation period of from three to six weeks one, or more often a group of papules appears in the skin over a developing granuloma, the granuloma usually rises up above the skin surface level, splitting the horny layer which is curled back the crater thus formed is filled with exudate which dries and forms a dome-shaped cap so that the lesion takes on the characteristic *mushroom* shape of the typical frambœside when this crust is removed the red raspberry like top of the granulomatous tumour will be seen at the base of the ulcer finally the crater is rapidly filled by more exudate and the crust reforms Several such ulcers coalesce

forming a single lesion an inch or even two inches in diameter There is usually an area of hyperæmia around the lesion and in dark-skinned subjects there may be a halo of hypopigmentation around this The lymph nodes in the neighbourhood are often enlarged and slightly tender The primary lesion is sometimes pruritic and in other cases painful, but usually it is both painless and non irritating

In some cases it is not possible to find any evidence of an initial lesion and in others a maculo-papular or even a macular spot takes the place of the granulomatous initial lesion

This initial lesion may continue to develop and may still be active when the secondary lesions appear but it usually then tends to heal, or on the other hand it may heal early so that there is only a scar to be seen when the second stage commences

This initial lesion is apparently not usually accompanied by any constitutional symptoms it is not however possible to be dogmatic on this point, as the people who usually suffer from this disease are not very intelligent, and would probably not notice or at least not report slight malaise.

The site of the primary lesions will vary according to circumstances depending as they do on the one hand on abrasions and on the other on contact with morbid material the lesions will be most common in the sites where these are most likely to occur as for example in mothers of infected infants they usually occur on the breast at the bend of the elbow and on the hip (*vide supra*) and in children on the lower extremities. Genital lesions are very rare and are placed as low as 2 per cent in some populations.

The secondary stage—The secondary lesions appear from six weeks to three months after the full development of the initial lesion The onset of the secondary stage is often associated with mild constitutional symptoms a low fever not often above 100 F joint pains pains in the bones and general malaise.

A large variety of secondary lesions is described and in the text books these make a formidable array that must alarm and confuse the student However the pathological processes that produce these lesions are, qualitatively at least, the same although they may vary in number in distribution, and in the extent to which they progress before resolution as well as being influenced by such variable factors, as for example individual and racial differences in skin texture

The individual foci may produce very minute papules with little keratosis and if these are arranged in groups they will give the appearance of macules or if they are slightly larger and very numerous that of a lichenous rash When these lesions resolve, they desquamate producing the furfuraceous desquamation that is described. If there is a little more keratosis a papular or papulo-macular eruption will result The majority of these papules will subside but some will continue to develop and the typical papillomatous frambœside very similar to the initial lesion will appear These yaws papules sometimes develop in the form of a ring with an area of unaffected skin in the centre this particular form is given the name ringworm yaws.

Finally when these lesions develop in the skin of the palms or soles on account of the great thickness of the epidermis there, the clinical results are very different from those in other parts of the body Many types of plantar and palmar yaws are described and given various and often vernacular names but amongst the commonest types are the vesicular or papular eruptions that lead to separation of the superficial layers of the epidermis or to an eczematous condition and the hyperkeratosis that leads to cracking usually of the soles, with the formation of painful fissures Another characteristic lesion is the very painful crab yaws of the soles

this lesion usually appears somewhat later than the other *secondary lesions* and partly for this reason it is often classified as a tertiary lesion due to gummatous formation in the tissues, it is however, usually a secondary lesion *in which the yaws* granuloma takes some time to force its way through the thick horny layers of the skin. These lesions are very painful and crippling before they break through, and afterwards they produce extensive granulomatous ulcers that, when they eventually heal up cause a crippling deformity of the feet known as clavus

The lesions appear *in crops*, so that there will often be lesions in all stages of development present at the same time. This will also mean that the order of development may not seem to be consecutive and, for example the furfuraceous rash may appear after a typical frambœside (from an earlier crop) has already developed.

Thus there are three *types of secondary lesion, the early diffuse* frambœsides of several types the typical papillomatous frambœside, and the late plantar or palmar lesions

Sites —The diffuse lesions that is the papular eruption the furfuraceous rash etc appear mainly on the trunk and the limbs, whereas the typical frambœsides appear most commonly on the face the limbs and the buttocks also on the trunk, neck, and perineum, but the scalp is very seldom affected, the junction of skin and mucous membrane (*e g* around the anus, the mouth and the alæ nasi) are the most favoured sites

Progress —The fully-developed typical papillomatous frambœsides vary from the size of a pea to that of a large walnut (3 to 4 cm.), but they will usually be present at all stages of development and healing. They may heal within a month or so or persist for years. When they heal either spontaneously *or as a result of treatment, they leave a white scar*, this scar may become pigmented in the course of time, or it may persist for life

The tertiary stage —Most of the lesions in this stage owe their association with yaws to the fact that they are common lesions in populations that suffer from yaws and amongst persons who although they give no history and show no other evidence of syphilis, have positive Wassermann and/or Kahn reactions it has however seldom been possible to prove the yaws origin of these lesions parasitologically and for this reason they are often looked upon as *allergic manifestations*

These lesions may appear at any time from one year to twenty years after the appearance of the secondary lesions. Amongst the earliest and most typical tertiary lesions are juxta articular nodules these are hard fibrotic swellings in the subcutaneous tissue around the joints they vary *in size from a pea to a pigeon's egg* they are usually attached to the ligamentous tissues of the joints or tendon sheaths but the skin is freely movable over them—at least at first, but later probably as the result of trauma it may become fixed, and they are *not normally painful but* from their position (usually on the outer side of the joint) are very liable to damage. The knees and ankles are the commonest joints affected, but the nodules may occur around almost any joint and similar fibrotic swellings are sometimes found in the subcutaneous tissue in other parts of the body

Gummata develop in the subcutaneous tissues and eventually ulcerate through the skin causing chronic septic ulcers

There are several types of bone lesion. *A soft painful swelling of* the periosteum particularly of the tibia and ulna that occurs relatively early in the disease is often classed as a secondary lesion. There is also an osteitis associated with severe gnawing pains that leads to bowing of the bones this occurs most characteristically in the tibia, producing the classical sabre tibia, or the boomerang leg of Australian aboriginals (Hackett, 1936)

but an osteitis also occurs in the bones of the fingers associated with a general dactylitis and later contractures, which causes the characteristic bowing of the fingers especially of the little and the adjoining finger Other bone lesions are a rarefying osteitis and gumma of the shaft which make spontaneous fracture a common occurrence

The keloid formations which are seen in different parts of the body and which often cause crippling contracture of the limbs should be looked upon as sequelæ rather than tertiary lesions as they are in most cases the direct result of earlier granulomata or gummatous formations in the affected areas although sometimes regular keloid scarring of skin surfaces *e g* the forehead or back is apparently spontaneous

There are certain atrophic changes in the skin and nails shown by the glazed appearance of the skin particularly of the palms, and by onychia and also disturbances in pigmentation particularly noticeable in the highly pigmented races that are almost certainly tertiary manifestations

There remain two clinical syndromes that are now recognised as being usually although perhaps not always sequelæ of yaws infection namely gangosa and goundou the former usually occurs in adults who have suffered from yaws in childhood but the latter often appears at an earlier date and affects children. The evidence for the ætiological connection between these diseases and yaws is almost universally accepted as complete but in only a very few cases has *Treponema pertenue* been isolated from the lesions The serum reactions are usually positive but in the later stages they may become negative The case depends mainly on the epidemiological association of the conditions with yaws and the exclusion of other ætiological factors

Gangosa or rhinopharyngitis mutilans.—This is a condition in which there is ulceration of the mucous membrane of the nasopharynx and nose which involves and eventually destroys the soft tissues cartilages, bones and eventually the skin working from within outwards until the whole mouth, nose nasopharynx, and antra form one large fungating cavity with a single large aperture, which is perhaps bridged by the remains of the upper lip Minor degrees of this condition may occur in which the process is halted either spontaneously or as a result of treatment before the destruction has been complete The condition was at one time associated with leprosy but the association has been definitely disproved, and, though syphilis is capable of producing similar destruction in the countries where this condition is common the evidence is against its having a syphilitic origin whereas they are all areas in which yaws is almost the rule in childhood.

Somewhat similar conditions may be produced by rhinoscleroma and by espundia (*q v*)

Goundou.—In this condition there is a bony exostosis of the nasal processes of the upper maxilla usually bilateral It is usually associated with severe headaches some nasal obstruction and a sero-purulent and sometimes blood tinged discharge from the nose The skin over the exostosis is normal and freely movable The tumour may obstruct the lacrimal ducts and interfere with the line of vision but does not encroach on the orbit or otherwise affect the sight

DIAGNOSIS

Clinical—The typical yaws lesions is so characteristic that it is unlikely to be mistaken for other conditions but many of the other less typical lesions may well be, and it will often only be possible to diagnose their nature clinically by their association with the typical framboeside.

Laboratory—From the primary and from many of the secondary lesions especially from the framboeside it is possible to recover the spirochæte without much difficulty

The spirochæte can be seen by *dark-ground illumination, by the Indian* ink method or after staining by Leishman s or Giemsa s stain by Tribondeau s silver nitrate method or by some modification of these stains (*see* p 242)

Differential diagnosis—Syphilis and leprosy are probably the two diseases with which yaws has been confused most frequently in the past but the protean nature of the manifestations of yaws makes it possible to confuse the individual lesions with those of almost any skin disease and of many ulcerative conditions *e g* pityriasis rosea versicolor and pilaris lichen planus acne vulgaris psoriasis ichthyosis impetigo contagiosa tinea eczema *of various forms* lupus *erythematosis* and vulgaris oriental sore and South American leishmaniasis ulcus tropicum veldt sore and septic varicose and malignant ulcers.

The joint pains in the earlier stages and the juxta articular nodules in the tertiary stage may suggest rheumatism and arthritis and the juxta articular nodules as well as the fibrotic nodules that appear on other parts of the body may simulate fibromatosis

TABLE

The following table gives the main points of differentiation between yaws and syphilis

	Yaws	*Syphilis*
Epidemiology	Primitive people	Civilized people
	Children under 14 years	Adults.
	Seldom venereal	Usually venereal
	Never congenital	May be congenital
Tropism	Epiblastotropic	Panblastotropic.
Primary lesion	Extra-genital	Genital.
	Variable but *usually typical framboeside.*	*Typical indurated chancre.*
	Glandular involvement —not constant and glands soft.	commonly shotty enlargement
	Wassermann and Kahn reactions —negative	often positive
Secondary stage	Typical framboeside and furfuraceous desquamation.	Rash sore throat, etc.
	Mucous membranes —not affected	often affected.
	Eyes unaffected	Iritis common other eye lesions may occur
	Alopecia —unknown	may occur
	Constitutional symptoms —slight	may be marked
	Wassermann and Kahn reactions —positive.	positive
Tertiary stage	Lesions superficial and obvious troublesome and crippling non-fatal	Lesions mostly of viscera subtle *often fatal.*
	Nervous and cardio-vascular systems —not affected (according to most authorities)	both affected
	Blood Wassermann —usually positive but may be negative	always positive
Para-lesions	Do not occur (according to most authorities)	Tabes and G.P.I may occur
	C.S.F Wassermann reaction —never positive	often positive.
Treatment	Does not respond to mercurial treatment.	Will respond to mercurial treatment.

PREVENTION

This disease is essentially one of uneducated populations amongst these it usually occurs only in those communities with the most primitive habits and mode of living and it does not spread amongst members of the poorest classes where they observe some—even the most rudimentary—code of hygiene and behaviour Education is therefore the first principle in prevention. This may however be too idealistic or at least too long term a policy for most circumstances and organized wholesale treatment of the population will in most circumstances be the best method to adopt. How this treatment can be provided will depend entirely on the special circumstances Where the people are easily accessible a system of permanent hospitals and dispensaries with doctors nurses and health visitors can be arranged but for isolated communities it will be necessary to have itinerant units that can move from centre to centre It has been shown that although a full course of injections may be necessary to ensure a complete cure (*vide infra*) by giving even one or two injections to each infected individual it is possible to reduce the disease in a population very considerably as well as to provide much relief to the infected individuals

It is unnecessary to discuss such obvious but in the circumstances totally impracticable measures as isolation and early treatment of abrasions

TREATMENT

This can be considered under the four headings (*a*) general (*b*) local (*c*) specific and (*d*) subsidiary

(*a*) **General treatment.**—There is little that need be said about general treatment it is obvious that a well balanced nourishing diet suitable clothing that can be changed daily warm baths hot demulcent drinks, regulation of bowels and so forth are ideal recommendations but under the conditions under which yaws usually has to be treated it will be impossible to apply them, and one will usually be quite satisfied if one can manage to give the specific treatment to all those that require it.

(*b*) **Local treatment**—More rapid healing will certainly be brought about if the lesions are bathed in some antiseptic lotion the writer has used mercurial lotion and acriflavine 1 in 1,000 but probably some of the newer antiseptics will be more effective For applications that can be given to the patient to apply mercury ointments again are probably most useful These will have the effect of reducing secondary infection and preventing the external spreading of the specific infection.

(*c*) **Specific treatment.**—The specifics are arsenic and bismuth There are three different lines of treatment which can be adopted according to the varying circumstances or perhaps judiciously combined namely (*i*) intravenous or intramuscular arsenicals (*ii*) intramuscular bismuth and (*iii*) oral arsenicals

(*i*) The most rapid and dramatic results can be obtained by neo arsphenamine (*e g* neosalvarsan) injections in doses up to 0.90 gramme for man, 0 60 gramme for weak or small men and for women 0.30 gramme for a child under 10 years and 0 10 gramme for a child under two years or on a weight basis 0 01 gramme (one centigramme) per kilogramme of body weight. A distinct improvement will be produced by the first injection and complete disappearance of primary or secondary lesions after two or at the most three injections but in a certain percentage of cases a relapse of the secondary or more frequently of the tertiary, lesions will occur and the general opinion now is that at least six injections are necessary to ensure a negative Wassermann—which should always be the objective—and the complete eradication of the infection Sulpharsphenamine and other trivalent arsenicals for intravenous and intramuscular use will be

preferred by some any of the preparations that are effective in syphilis will be found of value in this disease. On the American continent, mapharsen has been used extensively in recent years in doses of 0 04 to 0 06 grammes for adults, and 0 4 milligrammes per pound in children.

For young children and when large numbers of persons have to be treated in a short time or under difficult circumstances intramuscular injections will usually be preferable. The usual precautions regarding the administration of these toxic drugs will of course, have to be taken.

(ii) The effect of bismuth injections is not immediate at least six injections at weekly intervals should be given, but distinct improvement will follow a smaller number Bismuth salicylate in a 10 per cent solution (dose up to 0.2 gramme) sodium potassium bismuth tartrate suspended in oil (dose up to 0.3 gramme) and precipitated bismuth suspended in oil to make a 10 per cent suspension (dose up to 0.2 gramme) have all been used with good effect. The first injection should be about half the maximum dose, and the dose should be increased by 0.5 c cm. at each injection children are given correspondingly smaller doses

A watch must be kept for stomatitis and albuminuria.

Treatment with bismuth is unquestionably inferior to that with arsphenamine, but this form of treatment has the advantage of being very much cheaper There are several useful proprietary preparations of bismuth, e g bismostab and neotrepol which will be convenient if a single case is to be treated, but by their use on a large scale much of the advantage of low cost is lost.

(iii) There are several safe and effective arsenical preparations that can be given by mouth e.g stovarsol and carbarsone These must be given in the full therapeutic dose, 0.5 gramme twice daily for an adult, for 15 days, if further dosage is required an interval should be allowed of about a month before a second course is started Good results have been obtained with this treatment, but these oral drugs are definitely less effective than the parenteral arsenic or bismuth

Several combinations of these three forms of treatment have been suggested, but probably the most effective is a course consisting of two intravenous neoarsphenamine and six intramuscular bismuth injections at weekly intervals the arsenic and bismuth injections being given coincidently on the first two occasions, the cost of such a course is not very high.

To summarize, for efficiency parenteral arsenic is the drug of choice, for cheapness parenteral bismuth and for utility the special arsenical preparations given by mouth.

Whatever the treatment given the aim should always be the reversal of a positive Wassermann or Kahn reaction.

(d) Subsidiary treatment.—For the tertiary lesions, some workers have used potassium iodide by mouth in large doses, either alone or in combination with arsenic and/or bismuth, they claim that a more rapid resolution is brought about by this means.

For some of the tertiary lesions e g the juxta articular nodules, the contractures and goundou surgical treatment will also be indicated.

Prognosis—Even when the condition is left untreated spontaneous resolution will occur in a certain percentage of cases in both the primary (but probably rarely) and in the secondary stage, and the latter lesions usually last from six months to two years In neither of these stages does death ever occur as a direct result of the disease, and in both proper treatment will always produce a cure.

The lesions of the third stage may be life-long in their effect, and even if treatment is given there will usually be some permanent disabilities

here again, however death will seldom occur as a direct result of the lesions although quite often as an indirect one Death from septic pneumonia occurs sooner or later in most cases of gangosa

PINTA

Definition —Pinta (*mal del pinto* or carate) is a contagious disease that occurs in certain tropical countries in the western hemisphere it is characterized by papulo-squamous eruptions which may appear on any part of the body and which are chronic and eventually produce pigmentary disturbances and it is caused by the spirochætal organism *Treponema carateum*

Discussion.—Much has been discovered about this disease during the last few years but it is obvious that there is still much more to be learnt. Its ætiology has in the recent past been the subject of some imaginative writing regarding the different species of fungi of several genera, *e.g.* *Aspergillus* *Monilia* and *Trichophyton* that caused the red, white blue yellow purple and black lesions Several workers (Herrejon, 1927 and Fox, 1928) have for some years suspected the spirochætal nature of this disease on account of the response to anti-syphilitic treatment and the positive Wassermann reaction but up to five years ago (1938) the parasite managed to evade investigators.

The disease occurs in populations in which other skin diseases especially yaws are common this has led to many obviously inaccurate descriptions of the lesions of pinta appearing in the literature Recently writers have tended to describe three distinct stages of this disease as there are in syphilis and yaws this division appears to the present writer to be artificial, and he cannot help feeling that these writers are influenced by their desire to stress the similarity of pinta to the other recognized treponematoses. The evidence that some of the lesions described as tertiary manifestations and sequelæ of pinta are really caused by the *Treponema carateum* is wanting in view of the fact that syphilis or yaws is usually endemic in the same country

EPIDEMIOLOGY

Geographical distribution —The disease has a limited tropical distribution in the western hemisphere the main countries affected are Columbia (4 per cent of the population) and Mexico (11 per cent) but it also occurs in Cuba and other islands of the West Indies Venezuela Ecuador Peru Brazil and Central America. The endemicity of the disease has not been established in the eastern hemisphere though isolated and questionable cases have been reported from time to time in northern Africa, Iraq India Malaya and the Philippines.

The age incidence appears to vary in different countries and even in the same countries different observers give different figures most, however agree that pinta is rare in infants and uncommon in young children below five years of age. It seems probable that the commonest age of infection is in late childhood but that the lesions increase in number and potency so that superficial estimates indicate that the largest number are in the third and fourth decades whereas smaller and probably more accurate ones indicate an earlier age incidence.

People of the dark-skinned races seem to be more easily infected this is apparent in mixed populations.

ÆTIOLOGY

Historical.—The causal organism *Treponema carateum* was discovered by Drs. Triana and Armenteros, in the exudate from lesions and in the associated lymph nodules of a case of pinta in Havana, Cuba, in August 1938 this finding was confirmed two months later by Leon y Blanco These workers did not give the parasite a name this was done by Brumpt (1939) who called it *Treponema carateum*, which has priority over the name *Treponema herrejoni* given to it a year later by Leon y Blanco (1940) in honour of Dr Herrejon a [illegible] Mexican physician.

life. Although venereal transmission is possible the infection is usually transmitted non venereally Promiscuous sexual intercourse is uncommon in these tribes but cups, glasses, plates and towels are shared freely by the members of not only one but several families.

During certain seasons, flies are very prevalent and just as yaws can apparently be transmitted by *Hippelates pallipes* and pinta by *Simulium hæmatopotum*, so bejel may be transmitted mechanically by house-flies

Unlike syphilis, but like yaws and pinta bejel is never transmitted congenitally

Ætiology —The causal organism is morphologically indistinguishable from *Treponema pallidum T pertenue*, and *T carateum*, but, in the writer's opinion it is more flexible. The spirochæte is found easily in early lesions but is very scanty in the late lesions the former are presumably the most infectious Attempts to infect rabbits guinea pigs, and mice intradermally have so far failed.

Immunity —There is no natural immunity to bejel and persons of all ages and races are apparently susceptible but immunity can be acquired through previous infection thus most adult Arabs are immune through infection in childhood. The Wassermann Kolmer and Kahn reactions are constantly positive in this disease

The question of cross immunity between bejel and syphilis, yaws and pinta has not yet been settled, but the writer has seen syphilitic chancre develop in Arabs who had had bejel and who showed a positive Kahn reaction.

Pathology —This has not been studied to the same extent as in the other treponematoses but it is evident that this disease is an epiblastotropic one like yaws and pinta rather than a panblastotropic one, like syphilis.

The skin lesions are characteristically granulomatous ones

SYMPTOMATOLOGY

The initial lesions are usually in or around the mouth however in those rare cases where the infection is venereal the lesions are naturally on the genitalia. These initial lesions are usually patches which desquamate but do not ulcerate The usual location is the lips, angles of the mouth tongue, or mucosa of the cheeks rarely the glans penis labia or mucosa of the vagina. At the same time, or sometimes after a short interval papules appear on the trunk extremities groin and genitalia and develop into circinate and rarely roseolar eruptions. As there is never a history of anything corresponding to the primary chancre of syphilis, it seems probable that these constitute the primary lesions.

There are no constitutional symptoms, and no pain or pruritus in association with these early lesions and apparently the health of the child is not impaired. These lesions disappear spontaneously without leaving any scar, and often without any treatment.

A latent period is followed by the appearance of the late lesions which are usually ulcerative in character A small erythematous patch appears in the soft tissues of the mouth this breaks down and spreads to the soft palate tonsil or pharynx so that swallowing becomes painful. Leucoplakial patches may be observed in the mouth After several months the lesion heals with the formation of scar tissue. Sometimes the process extends to the larynx and produces changes in the voice or hoarseness or even stridor due to the contraction of a cicatrix. Similarly the ulcerative lesions of the nose may destroy the soft tissues and even erode through the hard palate into the mouth and maxillary sinuses producing a gangosa like condition and rarely paranasal swellings resembling goundou develop

The characteristic skin lesions begin as papules and then ulcerate these granulomatous ulcers heal in one place while spreading in another and at times fungating masses result that become covered with crusts and exude a sero-sanguineous or purulent discharge.

Hyperkeratosis of the soles of the feet either localized at sites which bear weight or generalized with extensive fissures are common findings There are similar lesions of the palms. Sometimes depigmented areas appear on the skin and there may be alopecia (Hudson, 1936)

Periostitis and osteitis, especially of the long bones frequently occur patients complain of throbbing bone pains and sometimes the small bones of the hands are involved Juxta articular nodules around the knee ankle and back are seen These are painless movable hard masses which do not have any tendency to ulceration but may become fibrosed (Hudson 1935)

There is either localized hypertrophy of the lymph nodes in the neck groin epitrochlear region or a diffused generalized lymphadenopathy Such glands are painless and freely movable They usually disappear altogether eventually

Apparently there are no cardiovascular symptoms but occasionally cases with invasion of the central nervous system have been reported with changes in the chemistry and cell count of the cerebrospinal fluid and a positive Kolmer and Kahn (Hoff and Shabey 1940) It should, however, be remembered that bejel and syphilis can probably co-exist Tabes and general paralysis are rare among Arabs

TREATMENT

The specific treatment of choice is neoarsphenamine. It must however be remembered that the Arab cannot tolerate large doses of arsenicals Bismuth comes next in its effectiveness while mercury also gives very satisfactory results A much shorter course of treatment than that given for syphilis is necessary

Prevention —The most effective means will be by education and propaganda amongst the tribesmen combined with a treatment campaign particularly amongst the children. Bismuth is the most practical drug for this on account of its relatively low cost and long-continued action but arsphenamine is more potent.

PROGNOSIS

This is good In many cases a spontaneous clinical remission will occur without treatment and the response to anti-syphilitic treatment is excellent

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TROPICAL SKIN ULCERATIONS

Introduction —There are many types of skin ulceration that will be encountered as frequently in a temperate as in a tropical climate specific

ulcers e g syphilitic, tuberculous, actinomycotic, and *glanders* ulcers associated with systemic or blood diseases such as diabetes sprue pellagra, sickle-celled anæmia and purpuric conditions non specific ulcers associated with varicose veins and septic ulcers secondary to skin diseases abrasions or wounds.

The ulcers especially associated with the tropics that have been described or will be described in other sections, include the cutaneous leishmaniasis oriental sore (p 178) and espundia (p 191), leprosy (p 481) yaws (p 524) cutaneous amœbiasis (p 435) tularæmia (p 345) rat bite fever (p 287), tsutsugamushi disease (p 276) and the venereal ulcerations lymphopathia venereum (p 552) and granuloma venereum (p 560), as well as the secondary ulcerations of bubonic plague and the rare cellulocutaneous type of septicæmic plague (p 321)

This leaves two tropical skin ulcerations that do not fall naturally into any other section, namely ulcus tropicum or Naga sore and veldt sore

ULCUS TROPICUM

Definition—*Ulcus* tropicum (Naga sore or so-called phagedænic ulcer*) is a troublesome lesion that occurs usually on the legs, amongst field workers mainly in humid tropical climates it is apparently caused in part at least by an anaerobic fusiform bacillus.

Geographical distribution—Ulcus tropicum occurs in many tropical countries, but the majority of the earlier reports on this condition came from Africa and India It is also common in tropical America

Epidemiology—It occurs almost exclusively in hot damp climates, and amongst farmers and field workers. It is more commonly reported amongst labour forces e g tea plantation workers in such countries but this is probably because of the financial loss to employers entailed as there is evidence that the private cultivator also often suffers from the condition. Recently a number of British and Indian soldiers in Assam have suffered from somewhat similar sores but it seems questionable whether these sores have the same ætiology

The disease occurs not only amongst men, but amongst women and children of both sexes in the population groups in which the latter also work in the fields

In the tea-estate labour forces in India ulcus tropicum reaches its peak of incidence at the beginning of the rainy season that is in June or July In most places there is a distinct seasonal incidence and, though the months of highest incidence may vary in different places it is nearly always a hot and humid season of the year

There is a marked variation in the incidence from year to year in any one locality this has been particularly noticeable on tea-estates

ÆTIOLOGY

A number of theories as to the cause of this condition have been put forward, with reference to which it is easier to be critical than constructive.

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* The word phagedænic (literally meaning eating canker or spreading ulcer) is not at all appropriate for the typical examples of 'Naga sore (named from its occurrence amongst the aboriginal tribes-folk in the districts around the Naga Hills in Assam) with which the writer has been familiar during the last 25 years, nor for many of the ulcers that he has either seen personally or had described to him first-hand in other places in India and elsewhere and which he has always classified in the same ætiological group When our knowledge, especially with regard to their true ætiology increases it will probably be possible to divide these ulcers into several groups. Meanwhile the writer has described the type with which he is most familiar

The subject can best be discussed under three headings the predisposing factor the specific organism and the determining factor

(a) The predisposing factor —There has been a strong tendency in recent years to attribute tropical ulcer to dietary deficiency in whole or in part The present writer (Editorial 1934) discussing the subject from the point of view of Indian experience suggested that dietary deficiency should be considered as a possible factor and Clements (1934) reporting experience in Papua observed that agriculturists living on a poor diet suffered more than fishermen on a much better high protein diet

Papers in which dietary deficiency is incriminated have never been very convincing or very specific in their indications as to which particular dietary element is the determining one several vitamins and calcium have been named Further many instances of the infection—natural experimental and accidental—of well nourished persons have been reported Nevertheless one must conclude after a general survey of the epidemiology that the state of nutrition of the subject possibly and even probably plays a part in the ætiology of this ulcer *

Again it would seem not unreasonable to suggest that debilitating diseases may reduce the individual's resistance against the invading organism and standard tropical infections such as malaria dysentery and ankylostomiasis have naturally been selected in fact at one time these ulcers were actually labelled malarial ulcers But there is no good evidence in favour of any one of these infections having any specific predisposing properties although it would be unsafe to deny the possibility that in a general way they all help to undermine the patient's resistance

(b) The specific organism —The frequency with which a fusiform bacillus alone or the fusiform bacillus *plus* a spirochæte are found in the wound again make the causal association between these organisms and the ulcer an obvious hypothesis These organisms are usually known severally as *Bacillus fusiformis* and *Treponema vincenti* although many writers believe that they are two phases of the same organism others in order to avoid taking sides in this controversy refer to the condition as fusospirochætosis In India we have found that the fusiform bacillus is constantly present and that there is always another organism almost equally prominent in the field this is however not always a spirochæte but is quite often a diphtheroid This view is not incompatible with the unitarian theory referred to above as in the instances in which there were no spirochætes in ulcers it may simply have meant that on account of some local condition in the ulcer all organisms were in the fusiform stage

The proof of the causal association of these organisms is not complete as it has never been possible to induce an ulcer with a pure culture of any of them although this has been done frequently with mixed organisms from an ulcer and with a mixed culture of *Bacillus fusiformis* and either diphtheroids or streptococci Further, fusospirochætal infections are found frequently in ulcers of the mouth and pharynx in venereal lesions and in gangrenous wounds of various localities

The fusiform bacillus is about 17 microns in length and 1 micron in thickness it is fusiform in shape as its name implies and it stains well with Romanowsky's stains usually showing a slightly beaded appearance. It is gram negative.

It is an anaerobe and can be grown on gelatin serum agar It would however be surprising if in the many tropical countries in which an

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Epidemiology —It occurs almost exclusively in hot damp climates, and amongst *farmers* and field workers. It is more commonly reported amongst labour forces e g tea plantation workers in such countries but this is probably because of the financial loss to employers entailed as there is evidence that the private cultivator also often suffers from the condition. Recently a number of British and Indian soldiers in Assam have suffered from somewhat similar sores but it seems questionable whether these sores have the same ætiology

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apparently similar ulcer appears there were not more than one specific organism concerned.

(c) **The determining factor**.—There seems to be very little doubt that some breach in the epithelium is essential to allow the organisms to gain entry Four common causes are (i) injury (ii) dermatitis (iii) insect or leech bite and (iv) water sores (ankylostoma invasion) The ulcer appears most commonly on the legs and feet at points most subject to injury in those who walk about bare legged on areas of skin likely to be affected by dermatitis as a result of coming in contact with irritant plants chemical manures etc or at points where hookworm larvæ often enter and cause vesiculation Panja and Acton (Acton 1932) showed experimentally that it was easier to produce an ulcer on the leg than on the arm in the latter situation a sore formed but healed rapidly whereas in the former it developed into a typical ulcer

It is often found that occupational groups particularly subject to local injury *e g* tea garden coolies working amongst tea bushes suffer more than their fellow coolies who work in the factory and even amongst Clements Papuan natives (*vide supra*) the factor may have been occupation rather than diet.

The source and transmission of the causal organism.—The fusiform organism is found infecting the mouth and other mucous membranes but it also occurs as a saprophyte widely in nature and is commonly found in the soil The ulcers appear in outbreaks in which a large number of persons are affected about the same time but it has never been satisfactorily demonstrated that one person is infected from another either directly or indirectly and it would be equally in keeping with the epidemiological observations to assume that they were all infected from a common source

Insects have been suspected as vectors but there is no indication that they act otherwise than as mechanical transmitters the common house-fly and flies of the genus *Siphunculina* have been particularly suspected. These latter flies are very prevalent at the season at which these ulcers occur and they are certainly attracted to purulent wounds but they have never been incriminated experimentally and some negative observations have been made It is almost certain that flies could act as mechanical transmitters how far they are responsible for outbreaks is uncertain and there is little positive supporting evidence for the hypothesis

Roy (1928) suggested that the bacillus probably remains in the soil just below the surface during the dry season and that when the first monsoon rains convert the surface soil into mud which is splashed and caked over the legs of the coolies or cultivators anaerobic fusiform bacilli which are included in the mud infect existing skin wounds. Later when the rains become heavy, the bacilli are washed out of the soil The present writer feels that this theory fits many of the known facts regarding the epidemiology of the disease It seems quite possible that the variations in the incidence of ulcus tropicum from year to year might be accounted for by variations in climatic conditions or in the use of manures which will alter the soil flora

PATHOLOGY

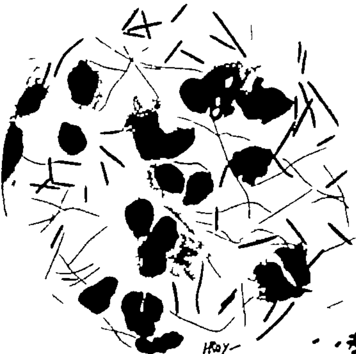
The fusiform bacillus is unable to establish itself without ... co-operation of some other organism the membrane-producing d... appear to be amongst the most suitable ... The fu ifor... multiply rapidly under the protecting ... d establish ... in subcutaneous tissues they have lim... of tissue ... they produce a toxin that causes nec... overlying cellular reaction in the surrounding ... there is

PLATE XIX



Fig. 1

Figs 1 and 3—Showing t
tropical ulcers in Assam tea-
labourers (R 1928)



Showing fusiform bacilli and spirochætes in a direct smear Stained with Giemsa.

Showing diplococci in a direct smear Stained with Giemsa.

Fusiform bacilli as seen in the gut of Siphonella 36 hours after ingestion

tion formation at the edges and in the base of the ulcer under the layer of [illegible] which form a thick mat immediately under the upper [illegible] layer of the ulcer; this granulation tissue is later replaced to some extent by fibrous tissue. There is some indication that the individual ulcer [illegible] self-limiting: the ulcer tends to be circular and not more than an inch or two inches in diameter; its downward extension is limited by the first fascial layer that it encounters, and its lateral extension by some cellular reaction and eventually by the fibrosis that occurs. There are of course occasions when two or several separate ulcers unite to form a large and continuous irregular-shaped ulcer which may almost surround the leg, interfere with the circulation and lymph drainage, and cause painful oedema of the leg and foot. There is no evidence of [illegible] or lymphatic extension, although the proximal lymph nodes may enlarge as a result of infection of the wound with [illegible].

SYMPTOMATOLOGY

Small itching papules appear at the site of an existing scratch or abrasion; these rapidly break down, or the necrotic tissue is removed, a small ulcer with undermined edges will be found underneath. The ulcer spreads rapidly and in a few days will have reached the standard size for a tropical ulcer, a circular ulcer from an inch to two inches in diameter. Other ulcers may in the meanwhile be developing in the neighbourhood; these may remain discrete or may coalesce and form a large ulcer. In a large percentage of cases there is, however, only a single circular ulcer.

The ulcers are usually on the lower limbs, on the dorsum of the foot, at the ankle, or in tops or on the front of the leg a few inches above the instep; they rarely occur above the knee (see plate XIX).

Mild constitutional symptoms of a toxaemic rather than a febrile nature often accompany the ulcers. Even deep ulcers may not be particularly painful, provided they do not interfere with the blood supply or lymph drainage, but when this occurs the swelling, heaviness, and pain make the patient unable, or at least disinclined, to do his work.

The discharge is usually a reddish watery exudate that trickles continuously from under the necrotic membrane that covers the ulcer. The edges of the ulcer at first are undermined, but later become firm, fibrotic, and raised. The ulcer extends down to the first fascial layer or to the bone, but the ordinary tropical ulcer does not usually involve the bone or the joints; however, the danger to joints from the presence of a large open septic wound in their vicinity is obvious, and in many cases the septic infection does extend to the tendon sheaths and joints, producing a dangerous condition at the time and serious crippling afterwards.

The ulcers are usually very chronic, but even without any special form of treatment most of them will heal up in a few months' time, in Assam for example when the rains stop and the weather becomes cool again. They leave a considerable scar. Any immunity that there is can only be very temporary, as it is not uncommon for a patient to suffer from these ulcers year after year at about the same season each year.

DIAGNOSIS

When tropical ulcers presenting the typical picture—circular sloughing ulcers with a firm raised edge exuding a sero-hæmorrhagic fluid and mostly below the knee—are seen against their appropriate epidemiological background, there should be no difficulty in arriving at a correct clinical diagnosis, but not even those most familiar with them should be prepared to make a diagnosis when an isolated ulcer is encountered in other

circumstances one must first exclude ulcers from other causes and finally resort to bacteriological examination.

Other conditions that have to be excluded are varicose ulcers (not common in the class of patient who is likely to suffer from tropical ulcer) syphilitic ulcers (which can be excluded by a negative Wassermann reaction) yaws (which can also be excluded by a negative Wassermann reaction and by failure to find *Treponema pertenue* in smears from the ulcer) oriental sore (which has a very different geographical distribution and is confined to drier climates and will show the round forms of *Leishmania tropica* in material taken from the edges of the ulcers see p 185) and veldt sore (from which true *Corynebacterium diphtheriæ* can be isolated)

If a smear is made from the exudate or better still from a scraping from the base of the ulcer the characteristic fusiform bacilli with or without spirochætes, will be recognized easily In a Giemsa stained specimen the characteristic beading of the fusiform bacilli will be clearly seen (see plate XX)

PREVENTION

As there is still some uncertainty about the cause of ulcus tropicum measures to prevent it cannot yet be placed on a proper scientific basis but if meanwhile we adopt certain premises it will be possible to map out a provisional preventive programme these premises are that the ulcers are most likely to occur in people who are ill nourished and/or debilitated from diseases such as malaria and dysentery that the causal organism—which is apparently a fusiform anaerobic bacillus—in nature lives as a saprophyte probably in the soil and that an epidermal lesion due to trauma, dermatitis water sores, insect or leech bite, or to some other cause, is essential for the specific organism or organisms to gain entry Preventive measures should therefore include (a) improvement of the diet and general state of health of the population (b) the protection of the limbs against direct contact with the soil or mud and the early cleansing of the skin thus contaminated (c) protection of the legs from trauma contact with irritant plants and insect and leech bites and the prevention of hookworm infection and of dermatitis from any cause.

How these recommendations are to be put into practice will depend so much on local conditions that detailed discussion here is out of the question Very careful consideration should however, be given before any special measures are adopted, as in the most promising theoretical recommendation there is liable to be a snag The point can possibly be best illustrated by quoting two recommendations made on *a priori* grounds that in practice failed.

(i) *Recommendation*—That a shallow concrete reservoir containing antiseptic lotion 16 inches deep be placed so that bare-footed tea-garden coolies returning from work have to walk through the tank and cleanse their legs.

Result—If the antiseptic was weak, it became neutralized after the first few dozen coolies had trailed through it with their muddy feet and the rest walked through a septic medium that was likely to spread any infection that already existed and if the antiseptic was strong, it irritated the legs of the first coolies that walked through it, causing dermatitis, and later became equally useless or detrimental

(ii) *Recommendation*—That tea-estate coolies should be provided with putties to protect their legs from scratches which they are very liable to get from the pruned tea bushes.

Result—Very early in the day the putties became saturated with rain and mud, and the wearing of damp putties for the rest of the day caused dermatitis.

It is possible that in certain circumstances both these recommendations might have been successful but in most cases they were a failure apparently for the reasons given above.

The encouragement and if necessary supervision of individual cleansing of the feet of coolies on return from work and the early treatment of all skin lesions may necessitate the temporary employment of considerable extra personnel on a tea estate but may be well worth undertaking if the efficiency of the labour force is seriou ly threatened at a time of year when most labour i needed a when there is a serious outbreak it often is

TREATMENT

There is no short cut to the treatment of this condition as is evident from the multiplicity and the variety of the treatment advocated Nearly every writer on the subject has some special treatment that he considers the best In view of the possibility that the name ulcus tropicum is used to describe an ætiologically heterogeneous group of ulcers short accounts of some of the treatments advocated by reliable observers will be included

Some Treatments Advocated

Specifics —Parenteral arsenicals arsphenamine neoarsphenamine, and novarsenobenzol can claim the largest number of advocates Various bismuth preparations have also been used apparently successfully

Sodium iodide given by mouth in doses up to the point of producing iodism combined with local applications of hydrogen peroxide has had some succes For sulphanilamide and sulphathiazole good results have been claimed by some workers and denied by others

A number of workers have advocated autogenous and specific stock vaccines prepared by various methods but others consider that as good results are obtained by stock non specific vaccines and yet others have recommended milk injections

Under thi heading also the specific action of calcium and of several vitamin that have been claimed by some—usually isolated—workers should be mentioned

Local applications —Neoarsphenamine and other arsenicals and sulphanilamide and sulphathiazole have been recommended as local applica tions A saturated solution of potassium permanganate (5 per cent) applied by means of a shaped piece of soaked lint to the ulcerated area only for as long as the patient can stand it pure phenol or powdered copper sulphate in glycerine (one part in two) similarly applied crude tar and powdered cinchona febrifuge have each been advocated More recently whole blood serum and powdered dry plasma have been advocated as dressings Some success has been claimed for cod liver oil dressings

For bathing the ulcers acriflavin 1 in 1 000 potassium permanganate 1 in 4,000 and electrolytic chlorogen have been advocated. Innumerable creams ointments and dusting powders are in use in the preparation of which zinc oxide several bismuth salts iodine, iodoform and/or sodium hypochlorite are combined with olive oil paraffin lanolin or boric acid

Surgical procedures from debridement to total excision of the ulcer have been advocated.

In considering the treatment of this condition it is very necessary to keep the practical aspects of the problem before one There will of course be other circumstances but a common one will be that in which a large number of coolies in a labour force are suffering from these ulcers and the immediate requirement i to get them on to their feet again in the shortest time possible In most cases it will pay in the long run to put the patient into hospital (and there will usually be some sort of hospital

however primitive) and treat him thoroughly rather than to apply pallia-tive measures

The patient must be kept lying down as much as possible The wound must be thoroughly cleansed, first with hot magnesium sulphate fomentations then preferably with hydrogen peroxide and finally with some antiseptic lotion such as eusol until the sloughs have been removed dead tissue can be cut away but any action to cause bleeding should be avoided The ulcer itself is then very carefully swabbed with pure phenol or with a mixture of copper sulphate and phenol in glycerine (half an ounce powdered copper sulphate in one ounce of glycerine to which a drachm of phenol is added) this is allowed to act for a few minutes and is then washed off with normal or hypertonic saline finally it is dusted over with sulphonamide covered lightly with a single or a double layer of gauze to keep off dust and flies but to allow as much air and sunlight as possible to get to the ulcer the latter appears to have a very beneficial effect in some cases This is repeated for several days until a healthy red healing surface is left One or two applications of scarlet red lotion may help the healing process After a week or ten days it will often be possible to cover the area with *tulle gras* or some such dressing strap the whole limb firmly or even put on a plaster-of paris casing and allow the patient to go back to work.

In some cases ambulatory treatment along these lines will be possible In such cases the phenol cauterization should be very thorough and the strapping or plaster should be applied and left for a week or more Some workers claim better results by cleaning the surrounding skin only putting on a piece of gauze and then applying the strapping or plaster immediately

Older ulcers with thick fibrous edges will require surgical scraping. This should be done under an anaesthetic and should be thorough it will also be advisable to swab the ulcer with phenol to complete the operation

If the area is extensive skin grafting will be necessary

During his stay in hospital the patient should be put on to a good balanced diet with a full quota of protein and additional vitamins if there are any other indications of specific deficiency

Prognosis—*Left untreated* a certain percentage of ulcers will heal in a month or so but the majority will continue for several months even up to a year or more

Under active treatment early ulcers should only keep the patient away from work for a few days more advanced ones for two to three weeks and very advanced ones for two to three months A few obstinate cases will be encountered that will lead to the loss of a limb and death may follow septic complications

VELDT SORE

Definition—Veldt sore is a shallow ulcer appearing on exposed parts of the body that affects white persons mainly in hot desert areas the Klebs-Loeffler bacillus is recoverable from the lesion in a large percentage of cases

Discussion.—The status of veldt sore as a distinct disease entity is not, in the opinion of the writer satisfactorily established This ulcer obtrudes itself on to the medical scene during war times—it made its debut in 1899 and staged come-backs in 1914 and 1939—and then retires into comparative obscurity from whence it is reported upon rarely often by non-medical patients and in retrospect It does not seem to have been investigated scientifically during peace interludes.

At the time of the Boer war bacteriology was young and *Staphylococcus aureus* was blamed during the first world war the Klebs-Loeffler bacillus was definitely associated with the disease but there was much about the aetiology and pathology still left unexplained and during the present war it is to be hoped

that the picture will be [illegible] The writer very much regrets that he has to write this chapter now and hopes that if this book ever goes into a second edition he will then be able to embody the fruit of recent experience

Skin infection with the Klebs-Loeffler bacillus is recognized in temperate climates and in the writer's recent and past experience diphtheroid and also true diphtheria bacilli have sometimes been isolated from several different forms of ulcer, especially ulcus tropicum but it seems unjustifiable on these grounds alone to call these veldt sores. The writer proposes to confine the discussion in this chapter to the shallow ulcer of desert areas while recognizing the fact that even these are probably a heterogeneous group

Geographical distribution —The condition has been reported from a number of localities mainly in the sub-tropics where desert conditions prevail South Australia (Barcoo river) Queensland North Africa including Egypt and the Sudan South Africa Gallipoli Arabia and Iraq and northern India

Epidemiology —The disease is largely confined to sojourners in hot desert areas e g Australians in the Barcoo river area it was prevalent amongst British soldiers in South Africa in 1899–1901 amongst the colonial and British troops in Gallipoli Egypt and Iraq in 1914–1918 and recently amongst the soldiers of the United Nations in North Africa

It is more common amongst fair haired than dark haired and commonest amongst red haired individuals it does apparently occur amongst the fairer skinned natives of the endemic area e g the Arabs of Iraq but is not common amongst these and is even rarer amongst darker skinned Africans and Indians

ÆTIOLOGY

Historical —W[illegible] (1918) noted the association of these sores with diphtheritic paralysis and Craig (1919) demonstrated the presence of Klebs-Loeffler bacilli in the lesions

Klebs-Loeffler bacilli (*Corynebacterium diphtheriae*) are recoverable from the well-established ulcer in a large majority of cases In the pre ulcer vesicular stage it is not usually found This suggests that the lesion in its early stages has some independent cause and that the diphtheria bacillus is superimposed and gives the ulcer its special character particularly its chronicity

What then are the predisposing causes of this lesion? A number of suggestions have been made Dietary deficiency sun trauma (Henderson 1943) and trauma and personal susceptibility of the fair and red haired In each case the data presented are suggestive but in no case convincing

PATHOLOGY AND SYMPTOMATOLOGY

The lesions usually appear on exposed and hairy parts of the body (*although not usually on the head*) on the dorsum of the feet on the knees on the back of the hands on the forearms and on face neck and ears A small vesicle develops at the root of a hair and gradually enlarges into a blister which eventually bursts leaving a shallow ulcer At first the base of the ulcer consists of the deeper layers of the epidermis but the infiltration extends into the dermis and the remaining epidermal layer sloughs off the ulcer extends centrifugally up to a maximum of about *two inches in diameter* At this stage the edges are punched out and slightly indurated and the base of the ulcer which is still shallow is covered with a greyish slough the surrounding skin is cyanosed rather than inflamed and there is not usually much exudate The lymphatic involvement is not constant and probably depends on the nature of the secondary invading organisms

The special character of the lesions is their obstinate chronicity and *their failure to respond to any of the usual treatments for septic sores*

They may heal temporarily with a thin epithelial covering which is likely to break down, and even when they finally heal they leave a depressed scar that may persist for years.

From the outset the lesion is a painful one at first the sensation is that of pricking and itching then burning and finally there is frank pain. There are usually some constitutional symptoms—fever headache and malaise.

Very common symptomatic associations with these ulcers which in one reported series occurred in 27 per cent of cases were the paræsthesias and paralyses that are frequently encountered in faucial diphtheria. Diphtheria toxin is absorbed at the site of the ulcer and passes along the nerve fibres to the central nervous system where it affects the motor cells and then diffuses to the neighbouring cells so that the first effects are noticed in the limb in which the ulcer is found weakness anæsthesia and paræsthesia of the leg and foot loss of knee jerk foot drop and loss of co-ordination and an ataxic gait are amongst the symptoms commonly encountered or if the sore was on the upper limb loss of power of grip, loss of tactile sensation and inability to execute any fine movements of the hand Later, the toxin reaches the circulation and more distant groups of muscles are affected such as the muscles of visual accommodation and of the palate.

The nervous symptoms do not usually develop for some weeks after the ulcers first appear and in fact it is often some weeks after the ulcers have healed before the eye symptoms develop

DIAGNOSIS

This is made on clinical and epidemiological grounds on bacteriological grounds or on both

The investigator must first decide for himself what in his opinion constitutes a veldt sore. He may decide to accept the clinical picture and epidemiological evidence alone if so should *Corynebacterium diphtheriæ* also be found the case will be nicely rounded off as showing a complete syndrome but their absence will not exclude a diagnosis of veldt sore in a clinically typical case seen in the appropriate surroundings. Or he may be more conservative and demand the typical clinical and epidemiological evidence and the Klebs-Loeffler bacillus On the other hand if he takes the view that any sore in which the Klebs Loeffler bacillus is found is a veldt sore then he must be prepared to revise his ideas of the epidemiology and clinical picture except with regard to the nervous sequelæ as he may, for example see typical Naga sores acquired in the humid jungles of Assam or Burma and starting perhaps as leech bites that will give an almost pure culture of *C diphtheriæ*

The writer feels that the first attitude is the correct one to take at present. Veldt sore was a clinical entity for many years then the Klebs-Loeffler bacillus was associated with it The Klebs-Loeffler bacillus has been shown to be promiscuous in its associations It does not seem logical to the writer that this bacillus should be allowed to take the name veldt into the humid jungles of Assam and Burma

PREVENTION

The initial sores can to some extent be prevented by giving exposed persons protection from the sun by suitable clothing and protecting ointments (*see* p 45) and from the irritating effects of sand and other trauma also by clothing and by frequent bathing and in view of the

possible effect of diet one mu t add by the giving of a balanced diet rich in vitamins

The superimposition of the diphtheritic infection can be prevented by early treatment and the protection of all sores and abrasions and in the case of troops or other communities by the discovery and suitable treatment of all diphtheria carriers

TREATMENT

The treatment of the early sores need not be di cu ed here, however when the Klebs-Loeffler bacillus is implanted in the wound anti-diphtheritic serum becomes a specific The serum is applied directly to the wound and about 4,000 units are injected into the tissues around the wound The effect i u ually dramatic

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LYMPHOPATHIA VENEREUM

Definition —Lymphopathia venereum (*syn.* lymphogranuloma inguinale and poradenitis) is a disease of venereal origin caused by a filtrable virus which produces a primary sore at the point of entry that is frequently overlooked infection of the inguinal glands in men and the pelvic glands in women and a series of conditions that have in the past been known severally as climatic bubo esthiomene or ulcer and elephantiasis of the genitals genito-recto-anal syndrome and '*inflammatory stricture of the* rectum

Historical.—Climatic bubo has for many years been recognized as a venereal condition common amongst and apparently peculiar to, sailors who have visited oriental and other tropical ports it was thus named by Godding in 1896. Materially the same condition but one with a slightly wider incidence was later described by Durand, Nicolas and Favre (1913) and the condition became known in France as *Nicolas-Favre disease* The troublesome chronic ulceration and elephantiasis of the female pudenda, sometimes associated with rectal stricture

and proctitis had been known to gynaecologists for nearly a hundred years (Huguier 1849) as esthiomene. Surgeons had long recognized an inflammatory stricture of the rectum in women the aetiology of which did not seem clear but which was common in prostitutes and often associated with venereal disease. It fell to microbiologists to correlate these independent observations of venereologists, gynaecologists and surgeons, and in 1930 Hellerström and Wassén and during the next two years Levaditi and his co-workers (1931) and Findlay (1932) showed that these were all caused by one and the same filtrable virus. The way had been cleared by Frei (1925) who introduced a specific test for venereal lymphogranuloma and climatic bubo. Stannus (1933) did much to draw attention to this group of diseases as a group by the publication of his book *The Sixth Venereal Disease*.

EPIDEMIOLOGY

Geographical distribution.—It has a world-wide distribution but it is undoubtedly much more common in tropical countries; this is probably less a matter of climate than of social conditions (*vide infra*).

Social, sex and race distribution.—It is a venereal disease. It is particularly associated with the low-class prostitutes that frequent dock areas in most countries in the world. The disease is very prevalent in Mediterranean, South American and Eastern ports where such prostitutes abound and where little or no control is exercised over them.

In a woman, evidence of the disease will often be concealed so that she may be unconscious of the infection and transmit it to a number of men; men are therefore more frequently affected. Further, for the same reason men will be more likely to seek medical advice and the sex disparity will be exaggerated.

In many places in the United States the disease is far more common amongst negroes than amongst members of the white populations. Vander Veer and his co-workers reported that 85 per cent of the cases at the Pennsylvania Hospital were negroes although negroes constituted only 37 per cent of the out-patient population. Further, Frei's test surveys indicate that a high percentage of the negro patients at venereal clinics suffer from this infection without necessarily showing any symptoms.

ÆTIOLOGY

Historical.—In 1924 Gamna described certain chromatin-staining bodies as being constantly present in macrophages in the lesion of lymphogranuloma inguinale; these are almost certainly inclusion bodies (*vide infra*). In 1930 Hellerstrom and Wassén proved that this disease was caused by a filtrable virus. Certain Japanese workers (Miyagawa *et al.* 1935–36) have satisfied themselves that the granulo-corpuscles, previously described by Gay Prieto (1927) and Findlay (1932–33), are actually the virus.

The causal organism is a filtrable virus between 0.127 micron and 0.175 micron in diameter; it passes through Seitz F and K, Chamberland 1, 2 and 3, and Berkefeld V and N filters. It is transmissible to most laboratory animals except rats. Mice are the most suitable experimental animals; in these animals an encephalitis is produced, and from the brains of infected mice an antigen has been prepared for Frei's test. It grows on the yolk-sac membrane of chick embryo, and from this source also an antigen has been prepared.

PATHOLOGY

The virus gains entry through a small abrasion in the skin or mucous membrane or possibly through the intact epithelium, usually of the prepuce or glans penis in men and of the vagina or the cervix in women, but in the latter the primary sore may be on or near the clitoris, in the fourchette or on the labia. Primary lesions around the anus and on the lips have

coloured races, are able to survive for many months and even years, but which eventually must lead to their death from sepsis and exhaustion.'

DIAGNOSIS

The clinical diagnosis in the well-developed and typical case should not present any difficulty but there will be many cases in which the syndrome is only partially developed, and in which a confirmation of the diagnosis will be welcome The finding of Gamna bodies and the granulo-corpuscles in histiocytes in biopsy material will provide some additional evidence, but these findings cannot be considered specific. It will therefore be necessary to do Frei's test to obtain absolute confirmation of existent, or at least recent, infection with the specific virus.

Frei's test.—There are four sources for the antigenic material for this test, namely, (a) aspirated pus from an inguinal or other bubo of a diagnosed case*, (b) macerated material from an infected gland, (c) mouse brain emulsion from a cerebrally infected mouse† and (d) emulsion of yolk-sacs inoculated with the virus. The first is probably the most satisfactory but it is very difficult to obtain uncontaminated pus in sufficient quantities and for this reason the mouse-brain antigen came into general use some years ago It is acknowledged that this gives less clear cut results and that it is necessary to measure the papules carefully and to compare them with a normal mouse-brain control to ensure a satisfactory result (Grace and Suskind, 1936) Sulkin *et al.* (1941) using a yolk-sac antigen prepared by McKee, Rake and Shaffer (1940) reported more specific results than they obtained with mouse-brain antigen A complement fixation test can be done with this same antigenic material this gives a very specific result.

The test becomes positive within 14 days of the first appearance of the primary lesion in a very large majority of cases rarely, the positive reaction is delayed for another week. It usually remains positive as long as there are lesions, and often for some time after they have healed. The test is positive in about 90 per cent of cases of chronic ulcerative elephantiasis of virus origin.

It has been shown that both the intradermal and the complement-fixation tests remain positive as long as the virus is present, and, conversely, if the reactions are positive, it is evident that the virus is still present. This may be as long as 25 years after infection, and it is possible that such persons are still infectious.

Technique.—An intracutaneous injection of 0.1 c.cm. of antigen is given into the skin of the arm or leg, and at the same time an injection of similar substance that does not contain the specific antigen is given a few inches away The result is read after 48 hours.

The result.—With Frei's pus antigen, a papule of at least 5 mm in diameter and with either the mouse-brain or the yolk-sac antigen of at least 7 mm., constitutes a positive result. The papule is surrounded by a hyperaemic halo and sometimes has a pustular or even a necrotic centre. The extreme limit of a non-specific reaction is 6 mm., and the controls are usually of the order of 1 to 4 mm. in diameter

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* To prepare this antigen, pus must be obtained by aspiration from an unopened bubo in a patient who has no other venereal disease This is diluted with four parts of saline, heated to 60 C for half an hour on three consecutive days and tested for sterility by aerobic and anaerobic technique If possible its antigenic properties are tested on a known case of the disease, after which it is ready for immediate use but can be kept for some time in the cold. A more satisfactory method of preserving the antigen is to freeze the pus and dry it *in vacuo* the powdered pus is dissolved in 50 parts of normal saline when it is required for use.

† Commercial preparations are available.

Precaution.—Frei (1938) recommends that the test should not be done in the prescute stage or in cases where there is suppuration near the perineum on account of the dangers of a generalized or local reaction.

This disease may be associated with other venereal diseases and when a diagnosis of some other venereal disease is made care should be taken to exclude the possibility that lymphopathia venereum infection has also been established Frei s test should therefore be a routine investigation in venereal clinics

Differential diagnosis —The buboes have to be distinguished from other glandular swellings acute enlargement *e g* sepsis, chancroid, glandular fever plague, and tularæmia and malignancy the elephantiasis and ulceration from filariasis and other causes of lymphatic obstruction, from granuloma venereum, chancroid cancer tuberculosis and actinomycosis and the rectal stricture from cancer syphilis tuberculosis ulcerative colitis and other dysenteries

PREVENTION

Under this heading it is only possible to make very general remarks. In this connection certain facts must be remembered Firstly lymphopathia venereum, unlike some other venereal diseases gonorrhœa and syphilis for example, is a disease that is confined to the lowest strata of society it is therefore obviously preventable by the observation of the simple rules of hygiene that people of the higher social strata observe. Secondly although there is every reason to believe that it is confined to the lower social strata it is not yet fully known how common it is, and whether there are not perhaps a certain number of persons with subclinical infections who act as carriers Thirdly it is a disease that has not received the attention that it deserves in medical schools or even in special classes on venereal diseases. Lastly there is as yet no treatment that can be considered a true specific for the disease.

The first line of attack must therefore be education primarily of general medical personnel then of the social hygienist and finally of the general public. In order to impress any of these groups with the importance of the subject figures will be necessary to obtain which not only is better reporting of the clinically obvious cases of this disease imperative, but clinically obscure cases must be sought out Frei s test surveys should be carried out in certain populations *e g* amongst prostitutes and should be adopted as a routine practice in venereal clinics. As satisfactory antigen is now obtainable commercially this should not present any great difficulty

Much can now be done by early recognition and treatment of the disease to limit its spread but if a sure specific could be found this line of attack would obviously be considerably facilitated

TREATMENT

In view of the diversity of the lesions, it is obvious that any adequate discussion on treatment would lead one far beyond the scope of this book, so that it will be necessary to confine remarks mainly to medical treatment.

No true specific treatment has yet been found some promising early reports on the use of certain sulpha drugs were published, but none of these drugs has lived up to this early promise which is not surprising in view of their total lack of success in other virus infections

There is evidence that in the early stages antimony will sometimes cut short the infection. The drugs used have been sodium antimony tartrate and fouadin or its chemical equivalents for dosage *see* GRANULOMA

VENEREUM Gold preparations have also been used but as their administration is not without danger and as their specific action in this disease is uncertain it seems unjustifiable to use them.

Earl (1939) reported good results with sulphapyridine 3 grammes daily for five days with a second similar course after four days interval, but few workers have had such good results with this small dosage With larger doses of either this drug or sulphathiazole (8 grammes followed by 6 grammes daily) continued for several weeks improvement appears to be effected in a certain number of cases The reversal of a positive Frei's test is evidence of cure.

In rectal stricture, considerable improvement in the secondary bowel condition is effected by placing the patient on sulphanilamide 3 grammes daily for 12 days alone or combined with 3 per cent 'sulpha' drug bowel washes When the inflammatory condition subsides the stricture disappears and it is often possible to avoid any surgical interference

The treatment by increasing doses of Frei's antigen that was advocated at one time was not a great success and has been largely abandoned

Buboes should be treated by local applications of heat infra red rays, or hot fomentations and later when they become soft and fluctuating they should be aspirated with a sterile syringe and sealed, rather than opened and drained

PROGNOSIS

Despite the absence of a truly specific treatment, if treatment is undertaken early the prognosis appears to be good This is especially true in the case of men. In uncomplicated rectal stricture when the pelvic adnexa are not involved to any extent, even when medical treatment has failed something can usually be done surgically In cases in which lymphatic obstruction is already established great care which may be difficult or impossible to maintain is necessary to prevent ulceration Finally when there is extensive ulceration with fistulæ already formed the condition is hopeless as the unhealthy tissues will not stand up to any plastic operations

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GRANULOMA INGUINALE

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Historical.—The disease was apparently first described by McLeod in India at the end of the nineteenth century The bacillus-like body now generally regarded as the causal organism was first associated with this disease by Donovan (1905) and has since been known as the Donovan body

EPIDEMIOLOGY

Geographical distribution—The infection is widespread in the tropics. It occurs in Brazil and other tropical countries in South and Central America in the West Indies and in the southern states of the United States, in tropical and northern Africa in southern China in India where it is confined mainly to the south-east coastal area, i.e Madras, with a few cases occurring in Bengal but none on the west coast, in northern Australia and in several Pacific islands.

Transmission—It is undoubtedly transmitted venereally as a general rule but there are exceptions to this rule, and there are certain anomalies which require explaining. It is, for example, often found in only one partner of a marriage. The explanation for this is that apparently it is only

infectious in its early stages In endemic countries it commonly follows circumcision operations even in children and other cutting operations, such as herniotomy in the genital area

Social, sex age and race distribution —More cases are reported in men than in women but, as in the case of lymphopathia venereum this may be that the early sores are often inapparent in the woman who may therefore transmit it to a number of men Children are frequently infected non venereally

The infection appears to be far more common in the coloured than in the white races and is confined largely to lower social strata, as is lymphopathia venereum but there are possibly more exceptions in the case of this disease which suggests that there is some common alternative mode of transmission of infection

ÆTIOLOGY

The Donovan body is constantly present in the tissues in the earlier lesions. It is a short (1 by 2 microns) capsulated bacillus-like body with rounded end but diplococcal forms are also seen It is found in large epithelial cells It was at an earlier date given the name *Calymmato bacillus granulomatis* but is now usually classified as *Klebsiella inguinale* (Bergey 1939) however in view of its marked host specificity (so far man only has been infected) its ability to reproduce only in living tissues namely in large mononuclear cells and its suggestive staining reactions many workers still believe that it is a protozoon or at any rate that it is not a Klebsiella It has also been suggested that the bodies may be cell inclusions and evidence of a virus that is the true causal organism.

It is gram negative but stains well with Romanowsky s stains and for this reason is often given in textbooks as likely to be confused with the round stage of leishmania and with *Histoplasma capsulatum* In the former case, there is very little similarity but the confusion might well take place in the student s mind on account of the similarity in the names the Donovan body and the Leishman Donovan body

Cultivation of the organism has been claimed by several workers but is not generally accepted, and this is certainly not a practical measure for diagnosis No lower animal is susceptible

Experimental transmission to man by rubbing the exudate from a sore on to the scarified skin has been effected

PATHOLOGY

The causal organism appears to be able to enter through the intact or at any rate very slightly abraded skin or mucous membrane. The first lesion to appear is a shallow ulcer that rapidly heals and it seems possible that this ulcer which is not constant, is caused by associated organisms. The typical cellular reaction is in the corium where there is first a round-celled infiltration followed by a typical granuloma formation with the formation of new capillary loops epithelial cells and fibroblasts there is thinning and later loss of the squamous layer in the central portion of the lesion but around the edges some epithelial proliferation and downgrowth of the inter papillary process sometimes suggesting squamous-celled carcinoma and at the base of the ulcer true granuloma formation with no endarteritis little tendency to necrosis, and no giant-cell formation. However in the dense fibrous tissue that is found in chronic lesions there may be pin point abscess formation as occurs in actinomycosis

The ulcer spreads by direct extension by auto-inoculation of apposed surfaces or indirectly by finger transfer of infection to more distant parts

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e.g the lips as the ulcer spreads in one direction the other end may hea leaving a track of white scar tissue There is no specific lymph nod infection

SYMPTOMATOLOGY

After an incubation period of a few days the primary sore appears, usually on the penis or in the groin in men, and on the labia in the fourchette or in the vagina in women. It is a shallow indolent and painless ulcer without any accompanying glandular enlargement It is easily overlooked, and in fact few women give any history of a primary sore It usually heals within a few days but after a few more days—making the total period ten days to three weeks from the time of exposure—one or more nodules may form in the same locality These break down and an ulcer appears on this occasion it is deeper shows no tendency to heal and spreads

The **typical granulomatous ulcer** develops there are three types of lesion, the sloughing ulcer with a purulent base but few granulations the granulomatous ulcer with the red velvety granulations rising to the skin level, that bleed easily, and the raised warty and purulent lesion These are not clean-cut types and not only are there intermediate types but one type may develop from the other, usually in the order mentioned If the ulcer is in the groin it usually extends rapidly the full length of the fold of the groin and to the root of the penis and scrotum and if it is on the penis it may spread down the penis for an inch or so and then by contact with an apposed surface *e g* in the groin or on the scrotum cause a new ulcer to develop

The ulcers become secondarily infected often with a fuso-spirochætal infection and usually emit a foul smelling sero-purulent discharge

In women the ulcer may spread up the walls of the vagina and involve the cervix. Or the lesion may commence as a chronic cervicitis

Transference of infection to other mucous membranes *e g* the mouth is not uncommon amongst persons with careless and unhygienic habits Rarely isolated extra-genital ulcers are found which suggest perverted practices

Very extensive areas of skin are sometimes involved. In course of time apparently as an attempt at spontaneous healing fibrotic changes occur at the edges of the ulcer and these sometimes extend into the ulcer isolating portions of it. These fibrous strands subsequently contract causing considerable deformities they also interfere with the lymphatic drainage, so that some degree of elephantiasis often occurs and, in the male it is not uncommon to see the penis and scrotum involved in a mass of fibrotic tissue and the whole glued to the inner aspect of the thigh and in women a condition not unlike that of esthiomene may occasionally result

Spontaneous healing of the whole ulcer may occur, but only with extensive scarring Scarring and keloid formation are particularly striking in negro patients In the dark-skinned races the scars are nearly always white and repigmentation seldom occurs.

Recently a most unusual case in which there were lesions on all parts of the body was seen in New Orleans. Some of the lesions on the back for example seemed to preclude direct or indirect external transfer of infection and suggested dissemination of infection *via* the blood stream.

To summarise there may or may not be a primary shallow ulcer otherwise the first lesion is a nodular button like one this is replaced by a spreading serpiginous ulcer which may develop a necrotic base but later becomes a hypertrophic granulomatous lesion and finally a cicatricial one. Extra genital lesions and even a generalized infection have been reported

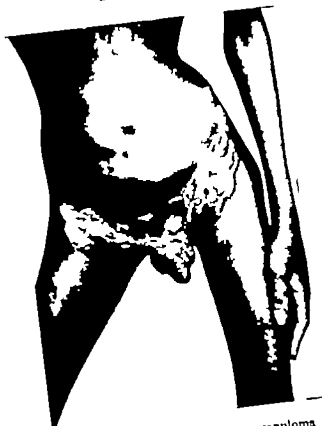


Fig 1—Showing extensive granuloma inguin l in both groins (R) m 1931)



Fig —S ic a fg 1 ft r tr t l w ll fou lm wh t -c only n ia n (Ra) 1931)



Fig 3—Showing a healed gra w ll exten i e s rring tl w th the l mph tic drain of the scrotum leg l t

by the use of a sitz bath this should be followed on each occasion by the application of a 20 per cent preparation of podophyllin in olive oil Should this application prove too painful it may be preceded by the application of some anaesthetic ointment (e.g pentocaine 4 per cent or anaesthesin) which should be allowed to act ten minutes before the podophyllin is applied (Tomsky *et al.* 1942) This should be continued for about a week—but the duration of the application will depend on the progress of the lesion—and then when the granulations are considerably reduced scarlet-red ointment applied to stimulate epithelial growth

As an alternative to podophyllin 4 per cent potassium antimonyl tartrate (tartar emetic) is used as before after the preliminary application of some anaesthetic ointment.

This local treatment may be applied without any specific treatment, but more rapid cure will be effected if the local and the specific treatments are combined.

(ii) Specific treatment.—Antimony preparations have proved the most successful. Many have been advocated but the most successful have been the simple potassium and sodium antimonyl tartrates and the more complex fouadin (pyro-catechin sodium bisulphonate B.P stibophen) More recently anthiomaline (lithium antimony thiomalate) has been used with limited success (Robinson and Robinson, 1942)

Fouadin is supplied in a 6.3 per cent solution in ampoules, and is given intramuscularly the initial dose is 1.5 c.cm. and the dose is increased by rapid stages to 5 0 c cm. if the patient shows no intolerance. The first three or four doses may be given on successive days but when the maximum is reached, 48 hours should be allowed between each injection. It is usually advisable to give a full course of about 50 c cm. and then to discontinue this treatment and observe the progress A second course may be commenced after two to three weeks interval or one of the other antimony preparations may be substituted. It is important to continue the treatment for some time after the lesions have healed as they are otherwise liable to relapse

The course and dosage with either sodium or potassium antimonyl tartrate is the same as that given in kala azar (*see* p 168) Anthiomaline is given in 2 c cm. doses of a 6 per cent solution from 12 to 15 doses usually being necessary

(iii) Surgical treatment.—Complete excision of the primary sore or the early secondary lesions is often possible, and should always be considered when an early diagnosis has been made but partial removal of a large lesion usually leads to infection of the wounds and extension of the process

Again, in the later stages after the specific organism has been destroyed as a result of the specific treatment there will often be a large raw surface left and it may be necessary to scrape or trim the fibrotic edges before the epithelium will begin to grow in from the margins and if the area is very extensive in order to hurry the healing process and limit scarring skin grafting will be necessary Further if important structures *e.g* the perineum, have been destroyed, or contractures have taken place plastic surgery will have to be considered.

Prognosis.—The earlier the treatment is undertaken the better are the chances of a rapid cure. With suitable specific trea ent the prospects are excellent in early cases and even in the more ... nes provided there are no serious complications and the patie ... operate cure and repair should eventually be effected but lef ... will continue to extend for ma years often caus ... the process eventually imperilling th ... e patient ... rippling an

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TABLE A

Phylum	Class	Sub-class	Order (or group)	Sub-order	Super-family	Genus	Species	
NEMATHELMINTHES	NEMATODA		Aphasmidia		Trichinelloidea	Trichinella	spiralis	1
						Trichocephalus	trichiurus	2
					Rhabditoidea	Strongyloides	stercoralis	3
						Ancylostoma	duodenale	4
					Strongyloidea	Ancylostoma	braziliense	5
						Necator	americanus	6
						Oesophagostomum	apiostomum	7
					Trichostrongyloidea	Trichostrongylus	spp	8
			Phasmidia		Oxyuroidea	Enterobius	vermicularis	9
					Ascaroidea	Ascaris	lumbricoides	10
					Spiruroidea	Gnathostoma	spinigerum	11
						Wuchereria	bancrofti	12
						Wuchereria	malayi	13
					Filarioidea	Onchocerca	volvulus	14
						Acanthocheilonema	perstans	15
						Loa	loa	16
						Mansonella	ozzardi	17
					Dracunculoidea	Dracunculus	medinensis	18
PLATYHELMINTHES	TREMATODA	DIGENEA				Schistosoma	haematobium	19
				Strigeata	Schistosomatoidea	Schistosoma	mansoni	20
						Schistosoma	japonicum	21
				Amphistomata	Paramphistomatoidea	Gastrodiscoides	hominis	22
			Prosostomata		Fascioloidea	Fasciola	hepatica	23
						Fasciolopsis	buski	24
					Echinostomatoidea	Echinostoma	spp	25
						Heterophyes	heterophyes	26
				Distomata	Heterophyoidea	Metagonimus	yokogawai	27
					Opisthorchoidea	Opisthorchis	felineus	28
						Clonorchis	sinensis	29
					Troglotrematoidea	Paragonimus	westermani	30
	CESTODEA	CESTODA	Pseudo-phyllidea		Bothriocephaloidea	Diphyllobothrium	latum	31
				(Super-family)	(Family) Taeniidae	Taenia	solium	32
						Taenia	saginata	33
						Echinococcus	granulosum	34
			Cyclo-phyllidea	Taenioidea	Hymenolepididae	Hymenolepis	nana	35
						Hymenolepis	diminuta	36

TABLE X—concld.

	Intermediate host or hosts	[illegible] (free-living habitat)	Definitive host (other than man) (reservoir)	Portal of entry: Method	Infective stage	Main site of development	[illegible]
1	Pig, rat, bear		Pig, rat, bear	M	[illegible]	[illegible]	[illegible]
2		Soil		M	[illegible]	[illegible]	[illegible]
3		Soil		[illegible]	Soil	[illegible] lines, [illegible]	[illegible]
4		Soil	Dog	[illegible]	[illegible]	Skin	[illegible]
5		Soil		[illegible]	[illegible]	[illegible] lines [illegible]	[illegible]
6		Soil		[illegible]	Soil	Skin lung [illegible]	[illegible]
7		?	[illegible]	M	?	[illegible]	[illegible]
8		Soil			[illegible]	[illegible]	[illegible]
9				M	[illegible]	[illegible]	[illegible]
10		Soil		M	[illegible]	[illegible]	[illegible]
11	Cyclops and fish	Water	[illegible]	M	[illegible]	[illegible]	[illegible]
12	Mosquitoes			[illegible]	[illegible]	[illegible]	[illegible]
13	Mosquitoes			[illegible]	[illegible]	[illegible]	[illegible]
14	Simulium			[illegible]	[illegible]	[illegible]	[illegible]
15	Culicoides			[illegible]	[illegible]	[illegible]	[illegible]
16	Chrysops			[illegible]	[illegible]	[illegible]	[illegible]
17	Culicoides			[illegible]	[illegible]	[illegible]	[illegible]
18	Cyclops	Water	[illegible]	M	Water	[illegible]	[illegible]
19	Snails	Water		[illegible]	Water	[illegible]	[illegible]
20	Snails	Water		[illegible]	Water	[illegible]	[illegible]
21	Snails	Water	Cattle, [illegible]	[illegible]	Water	Skin, lung, liver, [illegible]	[illegible]
22	Snails	Water			?	[illegible]	[illegible]
23	Snails	Water	Sheep	M	Veg	[illegible] liver	[illegible]
24	Snails	Water	Pig	M	Water, [illegible]	[illegible]	[illegible]
25	Snails	Water	Rat, dog	M	Snails	Small intestine	[illegible]
26	Snails and fish	Water	Cat, dog, fox	M	Fish	Small intestine	[illegible]
27	Snails and fish	Water	Cat, [illegible], pelican	M	Fish	Small intestine	[illegible]
28	Snails and fish	Water	Dog, cat, [illegible]	M	Fish	Liver [illegible]	[illegible]
29	Snails and fish	Water	Dog, cat, [illegible]	M	Fish	Liver	[illegible]
30	Snails and crabs	Water	Cat, dog, pig	M	Crabs	Lung	[illegible]
31	Fish	Water	Carnivora, [illegible]	M	Fish	[illegible]	[illegible]
32	Pig	Soil		M	[illegible]*	[illegible] muscle, brain, etc.	[illegible]
33	Cattle	Soil		M	Beef	[illegible]	[illegible]
34	Man, sheep		Dog	M	[illegible]*	Liver, lung, brain	[illegible]
35				M	[illegible]*	Small intestine	[illegible]
36	Arthropods		Rodents	M	[illegible]	Small intestine	[illegible]

* Indicates that the egg is the infective stage.

Pathology—The inability of most human helminthic parasites to complete a cycle of development within a single human host means that an helminthic infection is not susceptible to numerical increase within the individual host and that the weight of the infection, and therefore the extent of the pathogenesis will usually be dependent on the number of parasites that enter the host rather than on the tissue reactions of the host which so often are the determining factors in the production of disease by non metazoal parasites

The pathological responses of the host to helminthic infections are usually allergic rather than anti toxic in nature

Symptomatology—In the majority of helminthic infections the presence of only a few parasites will not cause pathological lesions of sufficient importance to produce clinical evidence of infection so that in circumstances of low endemicity the vast majority of the helminthic infections will be symptomless It is only when the initial invasion is *exceptionally heavy, or when the individual is subjected to repeated* invasions that these infections reach the clinical threshold and it is even less frequently that the diseases caused by helminths reach an acute stage Another result of this poor host tissue response is seen in the long duration of most helminthic infections.

Prevention—The complex life cycles of most helminths apparently display several Achilles heels but in practice it is found that these points are not usually as vulnerable as one would at first suppose, because of ingrained custom of the affected population groups To take some examples from the infections mentioned above hookworm infection could be obviated by proper sanitary disposal of fæces or by the use of sound footwear clonorchiasis and tæniasis by the avoidance of undercooked fish and meat dracontiasis by keeping wells covered or by drinking only filtered or boiled water filariasis by avoiding mosquito bites and so on but in each case it will be many decades and in some cases probably centuries before it will be possible to impress on the population groups most affected the necessity for altering their habits to fulfil these apparently simple requirements This establishes education and propaganda at the top of the list of preventive procedures against helminthic infections perhaps more firmly than in the case of infection by parasites of other phyla

Treatment.—In the treatment of bacterial and other infections we usually have to rely largely on the host-tissue reaction and are often content to stimulate or bolster up these rather than to attempt direct action against the parasite but in helminthic infections the relative poverty of the host tissue response complicates the treatment of these infections and makes it necessary to use drugs that act directly on the parasite and kill or narcotize it. In the case of the intestinal helminths this presents no great difficulty with the blood parasites it is more difficult, though some progress has been achieved but with the lymph and tissue parasites it presents a problem that has in no case yet been satisfactorily solved.

CLASSIFICATION

Some form of classification of helminthic diseases is desirable at least as a concession to the scientists' natural desire for order if not as an aid to memory for the student. Classification might be along several lines some of these will be considered —

I *Classification according to the taxonomic relation of the causal parasites*

These are shown in the table given on pp 568–9 From all the medical aspects of the subject, there are obvious limitations in the value of such a classification for example, the class Nematoda contains such divergent

species as *Enterobius vermicularis* and *Wuchereria bancrofti* the super family Trichinelloidea contains *Trichocephalus trichiurus* and *Trichinella spiralis* and the family Tæniidæ contains *Tænia saginata* and *Echinococcus granulosum* It is felt however that this table which gives an outline of the taxonomy of the majority of the human helminths (some of which are not deemed of sufficient importance to need further consideration in this book) may be of value for reference when the names of classes sub-classes orders, sub-orders and super families are mentioned by other writers It will also save the necessity for any further reference here to the subject of taxonomy

II Classification according to the medium of transmission and mode of entry of the causal parasite

In this classification, five groups can be considered —

(i) Oral infection with helminth eggs directly by contaminated fingers or other objects or indirectly through contaminated food This would include contaminated water supplies but water is not a common source of infection as helminth eggs are large objects and tend to sink rapidly so that any primitive form of sedimentation or filtration will remove them

(ii) Oral infection through raw food substances that contain encysted larvæ

(iii) Oral infection with water containing infected crustaceæ

(iv) Cutaneous infection by active entry of the pre adult forms (larvæ or cercariæ) from water In several instances the entry may also occur through the mucous membranes of the buccal cavity or pharynx but in no case is this the important route of infection

(v) Cutaneous infection by entry of larval form conveyed by arthropods

The arrangement of the important helminths according to this classification is shown in the table below —

TABLE B

Showing helminthic parasites arranged according to their portal of entry and the medium of transmission

Portal of entry	*Medium of transmission*	*Species*	
Oral	Fingers and contaminated food.	*Trichocephalus trichiurus* *Ascaris lumbricoides* *Œsophagostomum apiostomum* *Hymenolepis nana* *Echinococcus granulosum*	*Enterobius vermicularis* *Trichostrongylus spp* *Hymenolepis diminuta*
	Special food substances containing encysted larvæ	*Trichinella spiralis* *Fasciola hepatica* *Echinostoma spp* *Metagonimus yokogawai* *Clonorchis sinensis* *Tænia solium* *Diphyllobothrium l t m*	*Gnathostoma spinigerum* *Fasciolopsis buski* *Heterophyes heterophyes* *Opisthorchis felineus* *Paragonimus westermani* *Tænia saginata* *Gastrodiscoides hominis*
	Water containing infected crustaceæ	*Dracunculus medinensis*	
Cutaneous	Active invasion by larvæ or cercariæ from soil or water	*Strongyloides stercoralis* *Ancylostoma braziliense* *Schistosoma hæmatobium* *Schistosoma japonicum*	*Ancylostoma duodenale* *Necator americanus* *Schistosoma mansoni*
	Invasion by larvæ conveyed by arthropods	*Wuchereria bancrofti* *Acanthocheilonema perstans* *Onchocerca volvulus*	*Wuchereria malayi* *Loa loa* *Mansonella ozzardi*

III Classification according to the parasitological findings.—This is shown in tabular form below:—

TABLE C

Showing helminth infections arranged according to the clinical parasitic findings. A diagnostic classification

Stage	*Material*	*Species*	
Eggs	(i) In fæces (a) Constant, in large numbers.	*Trichocephalus trichiurus* *Ancylostoma duodenale* *Necator americanus* *Fasciolopsis buski*	*Ascaris lumbricoides* *Ancylostoma braziliense* *Trichostrongylus spp.*
	(b) Periodic or scanty	*Schistosoma mansoni* *Gastrodiscoides hominis* *Heterophyes heterophyes* *Opisthorchis felineus* *Clonorchis sinensis* *Diphyllobothrium latum* *Hymenolepis nana*	*Schistosoma japonicum* *Fasciola hepatica* *Echinostoma spp* *Metagonimus yokogawai* *Œsophagostomum* *Hymenolepis diminuta*
	(c) Rare	(*Schistosoma hæmatobium*) (*Paragonimus westermani*) (*Tænia solium*)	(*Enterobius vermicularis*) (*Tænia saginata*)
	(ii) In a peri-anal swab	*Enterobius vermicularis*	
	(iii) In the urine	*Schistosoma hæmatobium*	
	(iv) In the sputum	*Paragonimus westermani*	
Larvæ	(i) In fæces	*Strongyloides stercoralis* (*Trichinella spiralis*)	(*Necator americanus*) (*Ancylostoma duodenale*)
	(ii) In blood	*Wuchereria bancrofti* *Acanthocheilonema perstans* *Mansonella ozzardi*	*Wuchereria malayi* *Loa loa*
	(iii) In discharge from ulcers	*Dracunculus medinensis*	
	(iv) In subcutaneous tissues or muscle	*Onchocerca volvulus* *Trichinella spiralis*	
	(v) In cysts	*Echinococcus granulosus*	
Adult worms or proglottids.	(i) In fæces	*Tænia solium* (*Diphyllobothrium latum*)	*Tænia saginata*
	(ii) In subcutaneous tissues.	*Gnathostoma spinigerum* (*Loa loa*) (*Onchocerca volvulus*)	

Note.—The brackets indicate that the species also appears under another heading that is more important from a practical diagnostic point of view

Other classifications that might be adopted would be —

IV According to the nature of the intermediate host or hosts of the definitive hosts other than man and/or of the habitat of the free-living phase

V According to whether they are infections of warm or of temperate countries or are cosmopolitan in their distribution.

VI According to the main sites of the pathological processes that they engender

There is little to be gained by regrouping the worms according to these last three classifications but in the second half of table A these data are tabulated.

None of the above classifications would appear to be entirely satisfactory for the purpose of this book, but the following modification of VI the pathological classification seems to allow a consecutive presentation of the subject and has therefore been adopted here

CLASSIFICATION ADOPTED

A Intestinal parasites —These can be divided into several groups —

(i) Nematode worms whose portal of entry is the mouth whose infective stage is the egg whose cycle is a relatively simple one and does not include an intermediate host and whose distribution is cosmopolitan. In this group are included *Trichocephalus trichiurus Enterobius vermicularis* and *Ascaris lumbricoides* and they are described under the general heading Cosmopolitan intestinal nematode infections

(ii) Nematode worms whose usual portal of entry is through the skin, whose infective stage is the filariform larva, whose life cycle though it does not include an intermediate host, requires special exogenous conditions and whose distribution is mainly tropical. In this group are included *Ancylostoma duodenale Ancylostoma braziliense Necator americanus Strongyloides stercoralis* and *Trichostrongylus spp* though the usual portal of entry of the last named is not known it is apparently capable of entering through the skin or the mouth They are described under the heading Tropical intestinal nematode infections

(iii) The tapeworms *Diphyllobothrium latum Taenia solium Taenia saginata Hymenolepis nana* and *Hymenolepis diminuta* which are not a very homogeneous group in their life cycles though their portal of entry is in each instance the mouth and except in the case of *H nana* they enter in the larval stages they are cosmopolitan in their distribution They are described under the heading Tapeworm infections

(iv) *Trichinella spiralis* which must be considered here because the adult stage is in the intestinal mucosa and produces intestinal symptoms though the larval stage causes more serious symptoms in the same individual host Infection is by ingestion of the encysted larval stage in meat it is an infection of temperate zones. This is described under the heading Trichinosis

(v) The intestinal trematodes of which only one *Fasciolopsis buski*, is described here These worms have a complex life cycle they usually enter their determinative hosts in their larval stage and are tropical in their distribution (*Fasciolopsis buski* will be described more appropriately with the other flukes)

B Parasites of lymphatics subcutaneous tissues and serous cavities.—These can be divided into three groups —

(i) The filarioidea, *Wuchereria bancrofti Wuchereria malayi, Onchocerca volvulus Acanthocheilonema perstans Loa loa* and *Mansonella ozzardi* all of which gain entry in their larval stage by the agency of an

insect that acts as an intermediate host. They are described under the heading 'Filariasis'

(ii) The guinea worm *Dracunculus medinensis* which gains entry by mouth in a crustacean that acts as an intermediate host.

(iii) *Gnathostoma spinigerum* which apparently has a complete life cycle, including two intermediate hosts and gains entry by the mouth in the encysted larval stage in fish

All these infections have a tropical distribution.

C. Blood flukes.—The schistosomes *Schistosoma hæmatobium Schistosoma mansoni* and *Schistosoma japonicum* are the only three worms in this group Their life cycle includes intermediate hosts species of snails and they gain entry through the skin in their cercarial stage. They are described here under the heading 'Schistosomiasis'

D Liver and lung flukes.—Only two of these, *Clonorchis sinensis* and *Paragonimus westermani* are considered to be of sufficient importance to be described here. They gain entry in the encysted stage in food, and are tropical in their distribution. (The intestinal fluke, *Fasciolopsis buski* is also described here and the chapter is given the general heading Other fluke infections)

E. Worms that produce their main lesions in their larval stage.—These are *Echinococcus granulosum* whose larval stage only occurs in man and *Trichinella spiralis* and *Tænia solium* whose adult stages also occur in the intestines in man. In all three infection is by the mouth in the case of *Echinococcus granulosum* and *Tænia solium* (for the larval infections) in the egg stage and in *Trichinella spiralis* and *Tænia solium* (for the adult infection) in the encysted larval stage (In the two latter cases both larval and adult stages are described in their appropriate places amongst intestinal parasites)

COSMOPOLITAN INTESTINAL NEMATODE INFECTIONS

ASCARIASIS

THREADWORM INFECTION or OXYURIASIS

WHIPWORM or TRICHURIS INFECTION

ASCARIASIS

Epidemiology.—This is a cosmopolitan infection but, because the climatic conditions in tropical countries are more favourable than those in temperate and cold countries to the exogenous phase of this worm and because on the whole the populations of the former adopt a lower standard

of both personal and environmental hygiene the infection is a widespread and heavy one amongst the inhabitants of most tropical countries

Ascariasis is a good indicator of the degree of sanitary advancement in any population, and in temperate countries it is confined mainly to insanitary population groups and is particularly prevalent amongst poorer class children

ÆTIOLOGY

The causal organism—*Ascaris lumbricoides* is the only species of the genus to infect man. *Ascaris suis* of the pig is morphologically identical but physiologically distinct, and mutual interchange of hosts apparently does not occur

The egg is the infective stage. The fertile egg which measures 45 to 75 microns by 35 to 50 microns has a thick but transparent coarsely mammillated albuminoid shell it is unsegmented and it contains an almost globular protoplasmic mass of moderate-sized regular granules



Figure 140 The egg of *Ascaris lumbricoides* (fertile)

The larvæ develop inside the egg and pass through two stages before they emerge The larva that eventually emerges from the egg is 0.2 to 0.3 millimetres in length by 0 014 mm in diameter it passes through two more developmental stages and increases to 1 to 2 millimetres in length

The adults are large round worms the male is 15 to 31 mm. by 2 to 4 mm. in diameter and the female 20 to 35 mm by 3 to 6 mm but is occasionally longer

The life cycle.—Mature (embryonated) eggs are ingested in the duodenum the shells split and active embryos emerge these penetrate the mucous membrane of the intestine and enter a lymphatic vessel or venule* to reach the right side of the heart and the lungs in the blood stream in the lung the larvæ moult twice during a sojourn of several days and eventually they penetrate into an alveolus whence they migrate up the trachea and down the œsophagus to reach the intestine once more and become adult. In their larval stages they live on blood but the adults are almost entirely lumen

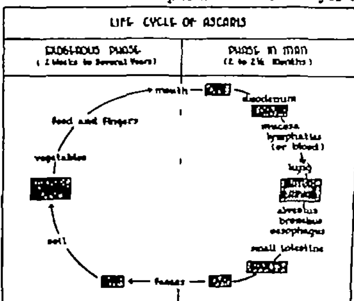


Figure 141

* There is experimental evidence for this (Ransom and Cram 1921) If however the larvæ (about 0.014 mm in diameter) travel via the venules, they will have to pass through the liver whereas if they travel via the lymphatics they sidetrack the liver There is no evidence of any damage to the liver but that caused to the lung is considerable It is possible that this is because they pause longer and undergo development in the latter organ or it may be that the large majority go by the lymphatics and miss the liver

feeders The female lays eggs at the rate of nearly a quarter of a million a day these are passed out with the stools and mature in the soil The adult worms may live for at least 15 months

Conditions favouring transmission—A moderately high temperature (30 C) favours the exogenous phase of the worm and though the eggs will survive drying and may be blown about in dust they reach maturity earlier in a warm humid environment

The infection is acquired from the fæces contaminated ground by means of soiled hands and other objects that children frequently place in their mouths contaminated food particularly vegetables in the growing of which human excreta have been used as manure and contaminated water supplies

PATHOLOGY

This is not a clear-cut a in many other helminthic infections

The migrating larvæ during their sojourn in the lungs damage the capillaries and cause a cellular largely eosinophilic reaction there is desquamation of the alveolar epithelium bleeding into the alveoli and often in heavy infections a pneumonitis or a true pneumonia resulting from secondary bacterial infection

Blood stained sputum containing ascaris larvæ may be coughed up

Aberrantly migrating larvæ may produce thrombotic lesions in various organs including the brain and the cord but such instances are rare

The adults in the intestinal canal do not cause any gross pathological lesion as a rule but when the infection is very heavy they may wander into other organs *e g* the gall bladder liver bronchus or even eustachian tube and produce considerable local disturbances or in the intestine itself they may become impacted causing obstruction, directly or as a result of intussusception and even perforation They also produce a toxin apparently an albuminose with neurotoxic anaphylactic anti peptic and other properties especially after they are dead that causes a local reaction in the bowel and is absorbed producing a toxæmia that may be fatal in ill nourished children

The writer has removed half a bucketful of worms from the intestinal tract of a patient who died of intestinal obstruction they were aggregated in solid knots in different parts of the intestinal tract. There were certainly a thousand round worms but the record is apparently held by Ryrie who counted 1 488 from one patient

Blood picture—There is usually an eosinophilia often up to 1,500 (or 20 per cent) per c.mm but the degree of eosinophilia is no indication of the weight of the infection

SYMPTOMATOLOGY

The symptoms produced are very variable in degree and very protean in character In the majority of light infections there are probably no symptoms due to the ascaris but some observers believe that in children even these light infections frequently cause intellectual retardation stunted growth and general sub-health

In heavy infections during the stage of migration the larvæ may undoubtedly cause pneumonitis and pneumonia and more rarely the conditions that result from embolism in the various organs and tissues referred to above

During their intestinal phase the adults cause vague abdominal pains indigestion nausea and vomiting malnutrition pallor (not necessarily associated with anæmia) and heavy rings under the eyes restlessness and

insomnia and in infants, convulsions and death as well as the *symptoms* produced by the worms when they wander into other organs *e.g.* suffocation when they obstruct the bronchi and peritonitis when they cause *intussusception* appendicitis or perforation

Children are very likely to pass live worms in their stools, or these may escape *per anum* between stools or be vomited, or escape through the nares the incident causes considerable alarm to the patient or the parent, but is not in itself of any special significance beyond indicating the presence of the worms and the probability that there are more.

Diagnosis.—The diagnosis does not ordinarily present any difficulty as the female passes large numbers of eggs regularly throughout her life and these can be readily recognised though it may be necessary to employ a concentration method Ascaris eggs are not well demonstrated by flotation methods. It is said that a certain percentage of persons less than 4 per cent, will harbour male worms only in such cases there will be no ova and a diagnosis will be best made by the therapeutic test.

The characteristic ascaris egg has been described above, but occasionally unfertilized eggs will be found these are longer and slightly narrower than the fertilized eggs they may or may not have the characteristic albuminoid shell and they contain a disorganized mass of highly refractile particles of various sizes

PREVENTION

All round sanitary improvement will be necessary to prevent or reduce this infection It will however be advisable to find out which are the most highly infected groups in a population and then what is the main source of infection so that special measures may be adopted. It is often a homestead problem in which the infection is maintained by promiscuous defæcation of children, and until this has been corrected, the infection will be certain to recur Education especially in schools will be an important means of achieving this

Mass treatment in which it will be most essential that all children are included, will effect some improvement by reducing the source of infection but unless combined with other sanitary measures it will not produce any permanent reduction in infection in the population

TREATMENT

Santonin which was at one time looked upon as a specific has little to recommend it, and has now been replaced by other safer and more efficient drugs.

Oil of chenopodium (B P) is very effective but is best given with tetrachlorethylene, 1 c cm of the former with 3 c cm of the latter for an adult and for children 0.25 c cm of this mixture for every year of *apparent* age. This should be given shaken up with an ounce of saturated sodium sulphate solution

For the safety of the patient it is essential to reduce the dose of oil of chenopodium as indicated above in the case of children but since the worms are the same size whatever the size of the host, the smaller doses may prove inadequate (Maplestone and Mukerji 1938) For this reason the less toxic hexylresorcinol may be substituted in the case of young children

Hexylresorcinol is at present available only in the form of the proprietary caprokol crystalloids (Sharp and Dohme) containing 0 1 gramme or 0.2 gramme each This is given on an empty stomach (5 hours after food) in doses of 1 gramme (5 × 0.2 gramme) for adults and older children

0.8 gramme for children between 6 and 11 years and 0 6 gramme for children from 1 to 5 years of age This dose is followed in two hours by an ounce of saturated sodium sulphate solution for an adult and less for children

In the case of either drug, if a good reaction is not secured within a *few hours* the purgative *should* be *repeated* as the early *removal* of both the drug *and* the dead worms is very desirable there is evidence that a toxin may be absorbed from the disintegrating ascaris

The full dose of the former medicine will usually cure 90 per cent of adults but with the smaller dosage in children the cure rate is not so high For the latter drug an all round 90 per cent cure rate i claimed

THREADWORM INFECTION or OXYURIASIS

Epidemiology —This infection is world wide it is also probably both the commonest and the most harmless of intestinal helminthic infections It has been shown to be present in 35 per cent of a general population group in Washington (D C U.S.A) and in nearly 70 per cent in certain *children s institutions* Writers usually assume that it will be *more common* in the tropics on account of the lower sanitary standards in these countries, but this is by no means a foregone conclusion as the habits and general mode of life of many inhabitants of the tropics are such that they would be less likely to foster this infection than are those of the natives of more advanced western countries However few reliable figures are available.

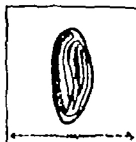


Figure 142 The egg of *Enterobius vermicularis*

As well as being an institutional disease it is a family disease. The highest infection rate will always be found in the children.

Ætiology —The casual parasite, *Enterobius vermicularis* (previously placed in the genus *Oxyuris* hence the name oxyuriasis ") is a very small thread like nematode worm the male, which is seldom seen, is 2 to 5 millimetres long by 0 1 to 0.2 mm. in diameter and the female which has a fine pointed tail is 8 to 12 mm. long by 0.3 to 0.5 mm. in diameter The eggs are 50 to 60 microns long and 20 to 30 in diameter they are ovoid in shape with one side slightly flattened they have a moderately thick transparent shell and when seen they usually contain a fully-developed embryo

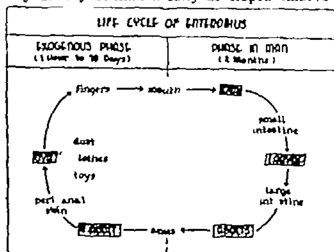


Figure 143.

Their life cycle is a simple one The eggs are swallowed larvæ hatch out in the duodenum and pass down the intestinal canal to the cæcum moulting twice *en route* here they develop into adults they attach themselves to the mucosa of the cæcum and large intestine but to oviposit the females migrate outside the intestinal canal. The eggs remain attached to the skin in the grooves around the anus to the

host's clothes or to the bedclothes or they fall to the ground where, when dry, they become part of the dust of the room and in an infected household can be recovered in large numbers from the dust lying on furniture or even along the tops of pictures on the wall The host may reinfect himself by scratching the skin around the anus or the eggs may regain entry into the same host or into other members of the family in innumerable ways and the cycle will commence again.

The cycle takes about two months to complete

Pathology and symptomatology—It is quite obvious that in the large majority of infected persons there is no pathogenesis There is no very convincing evidence that the worm produces any lesions in the intestinal tract, catarrhal inflammation, mucosal erosions and allergic manifestations in sensitive persons are referred to Acute and subacute appendicitis are sometimes mentioned in the symptomatology but the fact that the worms are found in 5 per cent of vermiform appendices (of which only a third showed acute inflammation) which are removed from members of a population with possibly a 35 per cent *Enterobius* infection rate is not very convincing evidence of the pathogenicity of this worm, or even of its predilection for this site

The female worm however causes anal pruritus which leads to scratching, and trauma, with the attendant dangers of secondary infection This will lead to disturbed sleep and irritability and may thus indirectly affect the health of a child

There is little evidence that in heavy infections in ill nourished children some invasion of the mucosa may take place, with resultant diarrhoeal and other disturbances but with this possible exception it seems very doubtful if any of the varied symptomatology that is popularly attributed to this worm is really caused by it

Diagnosis—Eggs will not be found in the stools of more than about 5 per cent of infected persons so that stool examination is useless To find the eggs it is necessary to take a swab from around the external anal orifice The best method of doing this is with the NIH (National Institute of Health) swab

Technique.—The NIH swab is essentially a glass rod rounded at the end which is capped by a piece of thin cellophane about one inch square this cellophane is held in place by a small rubber band. A useful alternative is a gummed cellophane strip For convenience of sterilization and transport, this swab is placed in a test-tube with the other end of the glass rod passed through the cork with which the test-tube is closed The cellophane swab is wiped around the anal orifice and the swab is replaced in the test-tube to be taken to the laboratory Here the swab is removed and the end placed and held on a large slide on which there is a drop of saline while the rubber band is pushed up the glass rod by means of a pair of forceps until the cellophane is released The rod is still held in position while the cellophane is smoothed out on the slide It is then removed a drop of saline is dropped on to the cellophane and a coverslip is applied. Under the low power the slide is examined and eggs will be seen lying between the slide and the cellophane and adhering to the latter

Prevention—The main source of infection lies in the patients themselves and the other members of the household and in their immediate environment Prevention therefore consists in simultaneous and thorough treatment of every member of a household combined with a very complete cleaning of the house and the maintenance of a high standard of personal cleanliness Such measures as providing night clothes that prevent children scratching their anal orifices and transferring the infection immediately to their mouths will limit massive reinfection but if the child is still infected reinfection will be *certain to take place* whatever precautions are taken and the problem will not be solved

Treatment —The most satisfactory results are obtained with gentian violet the dosage is the same as that for strongyloidiasis (see p 607) but it is usual to divide the course into two 8-day periods leaving an interval of one week between courses (Wright and Brady 1938) Hexylresorcinol is also very effective especially if the oral administration (for dosage *see* ASCARIASIS) is combined with an enema of a 1 in 1 000 dilution of the same drug After the morning dose of hexylresorcinol an alkaline enema is given and the bowel evacuated This is followed immediately by a high enema of one pint of 1 in 1,000 hexylresorcinol this should be retained as long as possible If the pain and/or tenesmus are severe even after evacua tion, a warm water bowel wash should be given

If the above drugs are not available tetrachlor ethylene a given in hookworm infection (see p 602) will be found relatively satisfactory

Whatever drug is used in order to test cure peri anal swabs should be taken It is un afe to assume that the patient is cured until seven such swabs (preferably NIH) have been negative

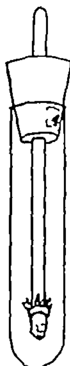


Figure 144 The NIH swab (Hall 1937)

WHIPWORM or TRICHURIS INFECTION

Epidemiology —This infection again is world wide but it is probably more common in the tropics especially the humid tropics It i epidemiologically closely associ ated with ascaris infection but is not so widespread and is less prevalent in dry area It i more common amongst children than adults

Ætiology —The causal parasite *Trichuris trichiura* (or *Trichocephalus trichiurus*) measures from 3 to 5 centimetres the male being slightly smaller than the female It is a whiti h grey worm with a filamentous anterior three-fifths and a stouter posterior two-fifths this gives it its very appropriate name The egg measures about 52 by 22 microns it has a double shell the outer one of which is bile-stained it is lemon-shaped and at each pole there is a hole through the shell that is filled with a *non staining* substance which like the bung in a barrel projects slightly to make button like prominences at each end

The life cycle is a follows —

Fully embryonated eggs are ingested by man who is the only host and the shell is dissolved off in the small intestine The larvæ that emerge attach themselves tem porarily to the local *mucosa* to obtain nourishment but soon pass on to the cæcum or the adjoining ileum or colon where they become adults The adults attach themselves to the mucou mem brane by their delicate head ends and some- times actually bury these for some distance just un ler the surface in a

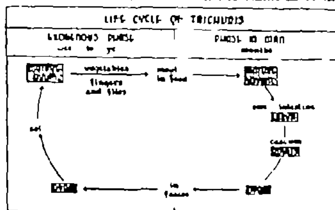


Figure 145

host's clothes or to the bedclothes or they fall to the ground where when dry they become part of the dust of the room and in an infected household can be recovered in large numbers from the dust lying on furniture or even along the tops of pictures on the wall. The host may reinfect himself by scratching the skin around the anus or the eggs may regain entry into the same host or into other members of the family in innumerable ways and the cycle will commence again

The cycle takes about two months to complete

Pathology and symptomatology—It is quite obvious that in the large majority of infected persons there is no pathogenesis. There is no very *convincing evidence* that the worm produces any lesions in the intestinal tract, catarrhal inflammation, mucosal erosions and allergic manifestations in sensitive persons are referred to Acute and subacute appendicitis are sometimes mentioned in the symptomatology but the fact that the worms are found in 5 per cent of vermiform appendices (of which only a third showed acute inflammation) which are removed from members of a population with possibly a 35 per cent *Enterobius* infection rate is not very convincing evidence of the pathogenicity of this worm or even of its predilection for this site

The female worm however causes anal pruritus which leads to scratching and trauma, with the attendant dangers of secondary infection This *will lead to disturbed sleep and irritability* and may thus *indirectly* affect the health of a child

There is little evidence that in heavy infections in ill nourished children some invasion of the mucosa may take place with resultant diarrhoeal and other disturbances but with this possible exception it seems very doubtful if any of the varied symptomatology that is popularly attributed to this worm is really caused by it.

Diagnosis.—Eggs will not be found in the stools of more than about 5 per cent of infected persons so that stool examination is useless To find the eggs it is necessary to take a swab from around the external anal orifice The best method of doing this is with the NIH (National Institute of Health) swab

Technique.—The NIH swab is essentially a glass rod rounded at the end, which is capped by a piece of thin cellophane about one inch square this cellophane is held in place by a small rubber band. A useful alternative is a gummed cellophane strip For convenience of sterilization and transport, this swab is placed in a test tube with the other end of the glass rod passed through the cork with which the test-tube is closed The cellophane swab is wiped around the anal orifice and the swab is replaced in the test-tube to be taken to the laboratory Here the swab is removed and the end placed and held on a large slide on which there is a drop of saline while the rubber band is pushed up the glass rod by means of a pair of forceps until the cellophane is released. The rod is still held in position while the cellophane is smoothed out on the slide it is then removed a drop of saline is dropped on to the cellophane and a coverslip is applied. Under the low power the slide is examined and eggs will be seen lying between the slide and the cellophane and adhering to the latter

Prevention—The main source of infection lies in the patients themselves and the other members of the household and in their immediate environment Prevention therefore consists in simultaneous and thorough treatment of every member of a household combined with a very complete cleaning of the house and the *maintenance of a high* standard of personal cleanliness Such measures as providing night clothes that prevent children scratching their anal orifices and transferring the infection immediately to their mouths will limit massive reinfection but if the child is still infected reinfection will be certain to take place whatever precautions are taken and the problem will not be solved

Treatment.—The most satisfactory results are obtained with gentian violet the dosage is the same as that for strongyloidiasis (see p 607) but it is usual to divide the course into two 8-day periods leaving an interval of one week between courses (Wright and Brady 1938) Hexylresorcinol is also very effective especially if the oral administration (for dosage see ASCARIASIS) is combined with an enema of a 1 in 1 000 dilution of the same drug After the morning dose of hexylresorcinol an alkaline enema is given and the bowel evacuated This is followed immediately by a high enema of one pint of 1 in 1,000 hexylresorcinol this should be retained as long as possible If the pain and/or tenesmus are severe even after evacuation a warm water bowel wash should be given

If the above drugs are not available tetrachlorethylene as given in hookworm infection (see p 602) will be found relatively satisfactory

Whatever drug is used in order to test cure perianal swabs should be taken It is unsafe to assume that the patient is cured until seven such swabs (preferably NIH) have been negative

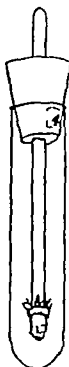


Figure 144 The NIH swab (Hall 1937)

WHIPWORM or TRICHURIS INFECTION

Epidemiology.—This infection again is world wide but it is probably more common in the tropics especially the humid tropics It is epidemiologically closely associated with ascaris infection but is not so widespread and is less prevalent in dry areas It is more common amongst children than adults

Ætiology.—The causal parasite *Trichuris trichiura* (or *Trichocephalus trichiurus*) measures from 3 to 5 centimetres the male being slightly smaller than the female It is a whitish grey worm with a filamentous anterior three-fifths and a stouter posterior two-fifths this gives it its very appropriate name The egg measures about 52 by 22 microns it has a double shell the outer one of which is bile-stained it is lemon shaped and at each pole there is a hole through the shell that is filled with a non-staining substance which like the bung in a barrel projects slightly to make button like prominences at each end

The life cycle is as follows —

Fully embryonated eggs are ingested by man who is the only host and the shell is dissolved off in the small intestine The larvæ that emerge attach themselves temporarily to the local mucosa to obtain nourishment but soon pass on to the cæcum or the adjoining ileum or colon where they become adults The adults attach themselves to the mucous membrane by their delicate head ends and sometimes actually bury these for some distance just under the surface in a

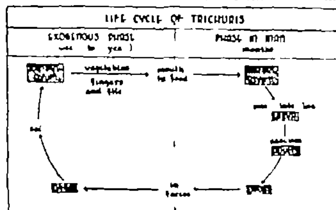


Figure 145

way that prevents easy mechanical removal Here the females produce their immature eggs which pass out with the stools on to suitable damp soil The developmental phase from egg to adult occupies about three months After about two weeks under optimal conditions they become mature. They are now ready for ingestion but will survive in a suitable medium for about a year and when they are ingested the cycle starts again

Pathology and symptomatology.—These worms appear to produce distinctly more damage in the intestines than do threadworms, and it is also believed that they suck blood. They are occasionally associated with a moderate eosinophilia which suggests the absorption by the host of some allergin and insomnia loss of appetite and nervousness are attributed to them even when infections are light but there is better evidence with regard to heavy infections, and it is believed that quite severe anæmia, diarrhœa emaciation and a condition somewhat similar to that produced by hookworm infection may occur

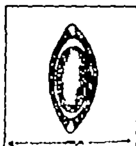


Figure 146 The egg of *Trichuris trichiura*

Diagnosis presents no difficulties The eggs can be found very easily in the fæces and are unmistakable Flotation methods will facilitate the search when the infection is light The number of eggs in the stools is a rough indication of the degree of infection.

Prevention.—There are no special measures to be recommended. This infection like that of ascaris is a good indication of personal and environmental hygienic practices of a community

Treatment.—There is no specific available for general use for the treatment of this infection. All the anthelmintics mentioned above should be tried. It is usually found that heavy infections are reduced by tetrachlorethylene and oil of chenopodium (*see* p 602) or hexylresorcinol but that light infections are often uninfluenced The results of treatment with any of these drugs will be better if the bowel is thoroughly washed out first by a saline purge and then a high alkaline enema.

There is however one substance that is apparently a specific namely leche de higueron which is the sap of certain species of the genus *Ficus* *Ficus glabrata* and *F doliaria* grow in Central and South America where they are used extensively as anthelmintics. The latex contains a proteolytic ferment but this can only be preserved under conditions of refrigeration and it is not yet commercially available outside the countries where it grows (Faust D Antoni and Sawitz 1943) In several countries *e g* India attempts have been made to use for this purpose the latex of the local species of *Ficus* but so far without success The fresh latex is given in a two-ounce dose on an empty stomach, preferably at night after a thorough cleansing of the bowel by salines and enemata

The cure is tested by examination of the stools for ova three to five days after treatment. If they are still present the treatment should be repeated after a week's interval.

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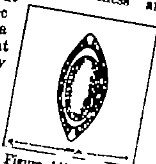


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a time but sheds it before it enters its new host. When it reaches the jejunum, the larva sheds its filariform cuticle attaches itself to the intestinal mucosa feeds and grows into an adult.

The adult worms are pinkish or creamy-grey in colour cylindrical slightly curved 8 to 13 mm in length with a greatest diameter of 0 4 to 0 6 mm the males are distinctly smaller than the females being seldom above 11 mm in length or 0.5 in diameter whereas the females are seldom less than 0 6 in diameter The worms of the other two species are slightly smaller *Necator americanus* varies from 7 to 9 mm. by 0.3 for the male and 9 to 11 mm. by 0 4 for the female and *Ancylostoma braziliense* is very slightly smaller than this but there is too much overlapping to allow the making of a diagnosis on size of the single individual alone, except of course where large ones—that are necessarily *Ancylostoma duodenale*—are encountered.

Hookworms are distinguished from other intestinal worms of about the same size by their dorsally flexed anterior ends and oval shaped heavily reinforced chitinoid buccal capsules In *A duodenale* there are two pairs of teeth and in *Necator americanus* a single pair of cutting plates.

The life cycle of the worm.—The eggs are passed in a stool by an infected individual on to the moist soil the stool is mixed with the surface layer of the soil by the action of rain by insects such as the coprophagic beetles or by animals within 48 hours the larvæ have emerged from the eggs the larvæ migrate laterally for only short distances measured in inches but in sandy soil may burrow for a foot or more below the surface of the ground Here they develop and when they have reached the third larval stage are infective to man Returning to the surface and lying on

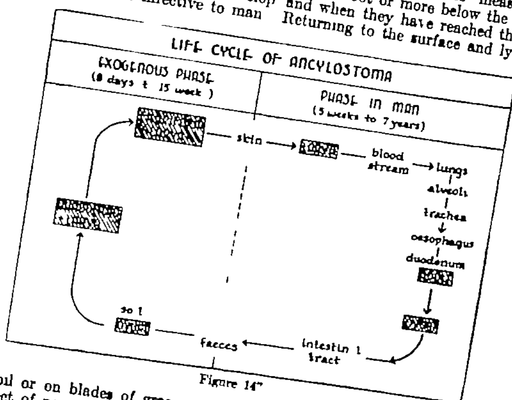


Figure 14

the soil or on blades of grass or other plants they attach themselves to the feet of passers by and immediately burrow into the skin, usually at the side of the foot on the dorsum or between the toes where the skin is thin and soft They will penetrate at any other site where the skin is sufficiently thin laboratory workers from Lo wards hav ly been infected through the hands as als ers and n

contaminated water are liable to be infected at any point on their skin surface.

The larvæ can penetrate the apparently normal skin either through the hair follicles or through microscopic faults in the epidermis they reach the blood vessels in the dermis, and, entering a venule they are carried in the blood stream *via* the right side of the heart to the lungs In the lungs they penetrate the wall of an alveolus and migrate *via* the bronchioles and the trachea to the epiglottis, in this migration they are aided by the ciliary epithelium of the respiratory tract. At the point of entrance into the air sac they cause a certain amount of local damage to the alveolar mucous membrane including localized hæmorrhages At the epiglottis they pass into the œsophagus and now reversing their direction they pass into the stomach and eventually reach the jejunum where they attach themselves to the mucous membrane and develop into male and female adult worms Not all the larvæ that start from the skin reach the jejunum some evidently die in the tissues

The adult worm is an avaricious and wanton blood sucker, that is it takes far more blood than it needs for its own nutrition literally pumping the blood out at the rate of 0 67 c cm. a day it has been estimated in the case of *Ancylostoma duodenale* *Necator americanus* takes less blood 0.2 to 0.5 c cm a day

The female worm lays her eggs in the lumen of the intestinal tract these have been variously estimated as averaging from 10,000 to 30 000 a day The egg output of *Necator americanus* is much less and is usually estimated at less than 10 000 a day

From the time the larvæ enter the body to the appearance of the first eggs in the stools there is an interval of about five weeks It has been estimated that 70 per cent of adults disappear from the intestine within a year nearly all within three years but rare instances of persistence up to nine years have been reported Thus although oviposition is believed not to be a continuous process it is fairly certain that a single female hook worm will produce several million eggs during her lifetime These are passed out with the fæces and the cycle begins again.

The viability of the ova and larvæ —If the eggs do not find their way into a suitable medium their development will be slowed down or stopped. In undiluted fæces they will survive for a long time but development is slowed in a septic tank they are destroyed in 40 days in a tropical climate In the larval stage in the soil provided the temperature and moisture are suitable they will survive up to 15 weeks They die if the temperature falls to 60 F or if the ground becomes excessively dry

Immunity —The question of immunity in helminthic *infections* is not yet placed on an entirely satisfactory basis but there is considerable evidence mainly based on analogy with helminthic infections in animals that immunity plays a far from unimportant part in the pathogenesis of helminthic infections in man There is epidemiological evidence that previous experience of hookworm infection provides some degree of protection against reinfection Further children in a community are always the most susceptible.

In dogs the development and maintenance of immunity is dependent to a large extent on their nutrition and when ill nourished dogs are given an adequate diet not only do they improve in health but they lose their hookworms and resist further infection (Otto and Kerr 1939)

In man the immunity appears rather to affect the larvæ during their migration through the host s tissues—the stimulation to antibody production being possibly provided by migrating larvæ that fail to reach their goal—than the adult worms in the intestinal canal and there is evidence

that the development of this immunity is dependent to some extent on the proper nutrition of the human host.

The effect of diet on the development of hookworm *disease* is of course a well-established fact, but this is not necessarily an immunity phenomenon.

It is a well-established fact that negroes are less susceptible to infection than white persons living under similar conditions. This is possibly due to their thicker skin. Conversely the thinness of the skin of children may also determine their greater susceptibility.

EPIDEMIOLOGY AND FACTORS IN HOOKWORM INFECTION

The essentials for the development of hookworm *infection* in a population are :—

(a) The presence of one or more infected persons as man is the only reservoir at least as far as *Ancylostoma duodenale* and *Necator americanus* are concerned.

(b) *A suitable terrain*, around a population unit—a *homestead* a coolie line or a village, a light soil, preferably a sandy loam, with decaying vegetation, and *shade or some other special local conditions, e.g. in a* mine or tunnel.

(c) Promiscuous defecation or at least a defective sanitary system.

(d) A warm humid climate (or micro-climate).

(e) A population that is largely barefooted in the hot months of the year at least, and is susceptible to infection.

For the development of hookworm *disease* one should add :—

(f) A sub-optimal diet for the population defective especially in iron and protein.

The subject may be discussed further under each of the above six headings.

(a) As has been indicated above a single pair of worms will during a year give rise to several million eggs which in a suitable medium will develop into a similar number of hookworms; these could theoretically cause a heavy infection in a large number of persons. In nature, however, the wastage is enormous, so that to maintain a high infection rate amongst the population a rich source of infection is necessary. Other *factors being equal* the infection amongst the population will vary with the degree of infection of the soil, which in turn will depend on the *number of infected persons polluting* the soil and the average number of ova in their stools. (b) and (c) Four examples under which these two conditions are optimal *for the development of hookworm* endemicity are given.

(i) *The small homestead of the "poor white" in the southern states of America.*—Here the land around the house is limited and therefore well trodden. Even if there is a privy *this may leak and/or be emptied carelessly* near the house, and the children of the household will often defecate promiscuously *elsewhere*.

(ii) *The village in India, e.g. in Bengal, Bihar or Assam.*—These villages are sometimes islands of slightly raised ground surrounded entirely by rice fields. There is usually no sanitary system and in the drier season *the villager defecates* in the open fields, often some lit ... r from the hou ... ot sun plays on the *stool all day and de* ... destroys some o ... or larvæ, and at night jackals eat what is ... hile it has not ... ly buried by dung beetles, even if the eg ... second intest ... (it has been shown that though the majo ... yed some su ... are at least taken further afield and there ... of their a ... contact with the feet of the villagers. H ... these fields ... as in many places they are for several ... ear the de ... nd becomes *confined to* a much smaller ... e house ... more abu ... Such ... ions favour the lar ... in the lo ... a fe ... lat ... the same indiv ... infect ... ber co ...

In other circumstances, the advent of the rains will tend to wash out the larvæ from the soil and most infections will occur in the dry season

(iii) *Tea estates in India.*—The tea-garden coolie is often a very primitive individual, who although he may have a latrine provided near his quarters prefers to answer nature's call when and where he hears it, which often means during his morning's work squatting between tea bushes he (or she) satisfies a small degree of modesty, avoids the eye of the overseer, and places the stool on the ground on which later he and his companions will have to stand while picking the tea leaves. In such cases the chances of both survival and re-entry of the larvæ are maximal

(iv) *Where human excreta are used as manure.*—This habit is common in China in particular and frequently comparatively fresh human excreta are used as manure The danger to the cultivator is obvious

Examples such as these could be multiplied indefinitely

(*d*) Hookworm infection is confined to hot countries except where in cooler countries the local conditions *e g* in a mine or tunnel simulate those of a hot country In sub-tropical countries during the months when the night temperature falls below 50 F larvæ will seldom be found in the soil and no infections will take place during these months *e g* in Alabama from December through March Similarly, in hot dry countries the larvæ die when the saturation deficiency rises above a certain figure but this figure depends to some extent on the nature of the soil in India Chandler (1927) found that 6 inches of rain per month were usually necessary to ensure transmission of infection

In humid areas on the other hand, Maplestone (1932) found evidence that the largest number of new infections were acquired in the warm months prior to the onset of the rainy season. When the rains started the ground became waterlogged and unsuitable for larval development.

In mines infection seldom occurs if the temperature is below 70 F and conditions only become optimal in the region of 78°F

(*e*) Shoes or boots, even if they are not defective, are not a complete protection against hookworm infection European planters in India or Indian overseers who have to walk through the highly infective mud in tea gardens although they may wear good leather boots frequently become infected but of course the infection rate is much lower than amongst the barefooted Indian labour The children in particular of the poor whites in the southern states of America usually go about barefooted at least in the summer time and in India and other eastern countries the majority of the labouring classes are always barefooted.

Miners in European mines at least usually wear boots or shoes but in these the infection occurs through the hands from the soil contaminated rungs of the ladders.

There is no evidence that there is such a thing in man as complete immunity to hookworm infection Negroes are not so readily infected as white persons in the southern states of America, but in India little difference in racial susceptibility has been noted Children appear to be more susceptible than adults. There is evidence that immunity is to some extent dependent on nutrition (*see* Immunity p 589)

(*f*) Whilst immunity to infection is uncertain there is no possible question about the effect of diet on the morbidity produced by the infection. The heavier the hookworm load in comparable population groups the higher will the morbidity rate usually be but this direct correlation between the hookworm load and the degree of anæmia for example in the individuals of a group is often absent This is probably a matter of individual differences in diet and iron assimilation. There is evidence that if the intake of iron is sufficient there will be no anæmia however heavy the hookworm load and further the writer has frequently been able to

show that even in the presence of a very heavy hookworm infection, it is possible to bring the hæmoglobin level back to normal by iron administration alone. Similarly, we (Napier and Das Gupta 1937) have shown that a high protein diet will produce a general improvement in the condition of patients suffering from hookworm disease causing the disappearance of the œdema.

Special circumstances and other factors.—Whilst the above discussion probably covers 99 9 per cent of hookworm infections there are exceptional circumstances under which infection may be acquired vicariously *e.g* in the laboratory and by bathing in water heavily contaminated by fresh sewage (Ashford *et al* 1933) Dogs, pigs and jackals commonly eat human fæces Some of the ova are destroyed in their intestinal tracts, but many survive so that these animals may act as disseminators of infection Cockroaches on the other hand have a digestion apparatus that destroys the ova and Chandler has suggested that in mines cockroaches should therefore be encouraged.

PATHOLOGY AND SYMPTOMATOLOGY

Variations in the clinical picture—The morbidity will depend on four circumstances—(*a*) the species of the worm (*b*) the duration of the exposure to infection that is, whether it was a single incident (acute) or a repeated one (chronic) (*c*) the weight of the infection, and (*d*) the tolerance of the host.

(*a*) **Species**—*Ancylostoma braziliense* the dog hookworm, frequently fails to reach the blood stream and so may produce only dermal lesions Although there are some localities where this species is capable of producing the full syndrome it is undoubtedly the least pathogenic of the three species Between the pathogenic potentialities of the other two species there is less difference, but *Ancylostoma duodenale* is the more pathogenic So that the ascending order of pathogenicity is *Ancylostoma braziliense* *Necator americanus* and *Ancylostoma duodenale* Mixed infections are common

(*b*) **Duration of exposure.**—The infection is usually a more or less continuous or at least an oft-repeated process but rare instances have been reported in which single heavy infections have occurred (Ashford *et al*, 1933) these latter have given us a valuable glimpse of the pathological processes that probably occur in all cases but which being as a rule spread out over so long a period have been difficult to appreciate clinically

(*c*) **Weight of infection and** (*d*) **host tolerance.**—The clinical picture shows considerable variation with the weight of the worm infection and the tolerance of the host In most areas the majority of infections are symptomless throughout while in others clinically apparent infections predominate The severity of the symptoms will on the whole, vary in the direct ratio to the weight of the infection but there will be many individual exceptions due to variations in host tolerance (*vide supra*)

Skin lesions.—At their point of entry the filariform larvæ cause a local irritation, no doubt partly on account of the organisms that they carry with them from their septic environment. As indicated above entry is usually at the sides of the foot, or on the dorsum between the toes where the skin is soft and thin. Within about half an hour of the entry of the larva there is a burning sensation and later the area becomes intensely irritating, a red weal forms there is local œdema and hyperæmia in the course of a day or two, the epidermis is raised in the form of small vesicles and the scratching that the irritation precipitates aids the introduction of septic organisms so that the vesicles burst and discharge their watery contents or become pustular These vesicles or pustules

which are usually multiple coalesce and finally an eczematous patch develops This condition is known as ground itch or water sores for obvious reasons

There is some evidence that this local condition is more frequently caused by *Necator americanus* than by *Ancylostoma duodenale* for it appears to be rare in Egypt where the latter only is found whereas in India where both worms are found it is relatively common especially amongst tea-estate labourers.

The pathology of creeping eruption is somewhat different as it is dependent on the fact that the larvæ of *Ancylostoma braziliense* the dog hookworm is often unable to penetrate all the layers of the skin after penetrating the epidermis, the larvæ wander laterally between the epidermis and the corium in an aimless manner for a considerable time causing a local reaction There is local infiltration by eosinophils and neutrophils with local hyperæmia and œdema, and later vesicle formation The worm then moves on the vesicles along its old tracks dry up and scabs form which later may be scratched off and the area secondarily infected It is usually very irritating The tracks of the larva can be seen easily through the epidermis like irregularly twisted threads they may move at the rate of several centimetres in twenty four hours and may produce extensive patterns throughout the skin surface of a limb They survive in this intradermal locus for several weeks or even months.

Occasionally the larvæ of the other species cause a similar condition

The larval phase—In synchronous heavy infections (acute) there is evidence that some larvæ do not immediately find their way into the venules of the skin but wander in the deeper tissues taking a month or so to reach the lung or perhaps never reaching it at all and being phagocytozed in the tissues. In such cases acute general symptoms *e.g* fever which may simulate typhoid and a sharp eosinophilic (75 per cent) leucocytosis have occurred. It is doubtful if in the ordinary spaced infection there is ever any trace of this syndrome beyond a moderate increase in eosinophils

The lung lesions.—The next point at which the worm makes its presence felt is in the lungs In escaping from the lung capillaries into the air sacs it penetrates the alveolar mucosa often causing submucous extravasations of blood, which may even reach the cavity of the alveoli and lead to collections of blood that are later coughed up by the patient Pneumonitis has been reported but is rarer than in the cases of ascaris and strongyloides infections In cases in which there is an acute that is a heavy synchronous infection, there may be a sensation of obstruction in the throat with difficulty in swallowing and speaking but in the ordinary case, in which the invasion is spread over a long period it is seldom possible to get any such history In acute cases these bronchial symptoms begin to appear as the skin symptoms subside that is to say at about the end of a week after exposure.

Gastro-intestinal symptoms—In the acute case these are usually pronounced there being marked gastro-intestinal discomfort, colicky pains and diarrhœa often with the passage of frank blood and mucus or of black tarry stools Even in mild infections in Europeans epigastric discomfort is a common symptom it often persists and may be the only evidence of the infection In heavier infections that have been spread over a long period especially in poorer class Indians and other barefooted populations these gastro-intestinal symptoms stand out from the rest of the picture of ill health The diarrhœa may be due to the local irritation and the absorption of metabolites in the intestine but Ashford and his co-workers (1933) believe that it may be the result of helminthic

metabolites from the live or dead larvæ that have gone astray in the tissues (vide supra)

In the acute case if there is no further infection the acute symptoms will tend to subside as the adult worms settle in the jejunum, but if the infection has been a severe one and the worms are not removed, anæmia will develop as the iron reserves of *the body are depleted and other* symptoms (*vide infra*) will appear It is scarcely conceivable that a single acute invasion that was non fatal in the earlier stages could produce *very serious chronic* manifestations however where the infection is a continuous process these earlier symptoms will be relatively insignificant but the symptoms of the established disease will be the important ones

General symptoms in established (chronic) ancylostomiasis.—When the adult worms are established in the jejunum, they suck blood possibly inject some toxin and make *small lesions in the mucosa which may* allow septic absorption The recognised syndrome of ancylostomiasis will now develop

The fully-developed ancylostomiasis syndrome shows a patient with œdema of the extremities and face—the puffy pale ancylostomiasis facies—mucous membranes almost white hair scanty and a protuberant abdomen. The patient has a vacant expression he has no energy and is indifferent to his surroundings. He complains of palpitations and is breathless on exertion *He suffers from dimness of vision and night blindness* Examination shows that his heart (both right and left side) is extremely dilated there is usually a mitral systolic murmur, and sometimes one at the pulmonary base his pulse is rapid and his blood pressure low His tongue has a wash leather appearance and often a black streak down the centre A watery diarrhœa is common

The cardiac changes which are all secondary to severe endocardial damage that is in turn caused mainly by the anæmia are easily reversible when the blood picture is improved by anti anæmic treatment alone, but there are a few cases in which this improvement will be delayed until the worms are expelled this suggests a possible second factor of a toxic or *an allergic nature* (Heilig, 1942)

Patients will usually have taken several years to reach this miserable state and in the case of children their physical and mental development will have been retarded so that a child of 16 years of age may physically and mentally appear to be no older than 10 years and at the same time he will lack the childish energy and desire to play with other children. Sexual maturation is also retarded A curious craving, manifested by geophagy (or eating of earth) often develops

The anæmia is perhaps the most striking morbid change and it is certainly the most easily measured so that the blood picture will be discussed in some detail.

***Blood picture** The cause of the anæmia.*—Until a few years ago there was much difference in opinion on the actual cause of hookworm anæmia. It is now well established that it is a true secondary anæmia due to the adult worms continuously pumping large quantities of blood from the host's circulation into the lumen of the intestinal canal. The lost blood has to be replaced and this can only be done at the expense of the reserves of iron and probably other blood forming substances Even with a heavy load of worms anæmia can be prevented, or even cured, by giving the patient a good protein diet *plus* medicinal iron but in persons living on the border line of iron starvation anæmia will be caused by quite a moderate load.

While *most cases can* be cured by iron administration alone (*vide infra*) there are a few exceptions in which the normal blood level cannot

be regained without the removal of the worm this suggests that the worms may also introduce some toxin or allergin that depresses hæmopoietic function However in a small series of cases in which a large number of blood examinations and sternal punctures were done the writer (Napier Das Gupta and Majumdar 1941) failed to see any evidence of the repressive effect on the bone marrow of the hypothetical toxin and we suggested that these few exceptions might be the result of malabsorption of some essential blood forming element as a result of course of dysfunction caused by the hookworm infection

The nature of the anæmia.—A more striking reduction in hæmoglobin can occur in hookworm disease than in any other disease of equal seriousness The writer has seen tea estate coolies walking into the dispensary with a hæmoglobin percentage that was estimated by the tea estate doctor at 5 per cent on the Tallqvist scale The blood that came out when one pricked the finger of such patients was a thin watery fluid which would not make a proper smear even on a scrupulously clean slide The colour was in fact well below the 10 per cent matching on the Tallqvist scale and by more accurate methods a figure of 1 5 grammes of hæmoglobin per 100 c cm. of blood was not an unusual finding with 900,000 red cells per c.mm. and a packed cell volume of 6 per cent this gives a mean corpuscular hæmoglobin (MCH) of 16 7γγ a mean corpuscular volume (MCV) of 66 1 cu.μ and a mean corpuscular hæmoglobin concentration (MCHC) of 25 0 per cent It is thus a microcytic hypochromic anæmia The picture is nearly always a microcytic hypochromic one but of course the anæmia is not usually as extreme as in the example quoted

There are usually a few normoblasts present and 2 to 5 per cent of reticulocytes the van den Bergh reaction is negative

There is often an increase in blood volume this compensates to some extent for the extreme anæmia and possibly explain why patients can live and even work with such low percentages of hæmoglobin There is a decrease in the serum proteins and in both calcium and cholesterol

The white cell count —The total count is usually between 5,000 and 10 000 per c.mm that is more or less normal but the eosinophil percentage is usually raised. An average count of 14 per cent is not unusual but in the very heavy infection the count is often within normal limits or eosinophil may even be absent

Gastric acidity —There are conflicting statements in the literature on this subject We found in a series of 28 Indians that the gastric acidity was normal or increased in 21 (or 75 per cent) and that the relation between the hookworm load and low gastric acidity was if anything a negative one, but that there was some relation (though not a significant one) between gastric acidity and hæmoglobin percentage suggesting that hookworm infection did not cause achlorhydria but that achlorhydria was possibly an independent contributory factor in the cause of anæmia. There were in this series only three cases of complete achlorhydria Anti anæmic treatment causes no striking improvement in the acidity

Fæces.—The stools are watery As well as the ova which will be discussed below there is nearly always occult blood

DIAGNOSIS

In the parenteral phases —The diagnosis of the ground itch would be difficult without the epidemiological background and the condition is likely to be confused with the secondary pyogenic invasions in tinea infections and other skin conditions but creeping eruption produces a map-like effect on the skin that is very characteristic *Gnathostoma spinigerum* and the larva of flies of the genus *Gasterophilus* may produce

somewhat similar conditions However both of these are more liable to cause deeper tunnelling and abscess formation, though the diagnosis can be made with certainty only by the recovery and identification of the worm or the fly maggot from the lesions There is little opportunity to make an accurate diagnosis at any other stage of the parenteral infection, although in a few cases larvæ have been coughed up from the lung

In the intestinal phase.—The clinical picture of hookworm disease is a characteristic one and so also is the anæmia (*vide supra*), but it would not be justifiable to make a diagnosis without the confirmation of stool examination The finding of hookworm ova in the stools is evidence of *hookworm infection* but, even when the ova occur in relatively large numbers and the patient is anæmic this is not necessarily evidence of *hookworm disease* as the anæmia may have some other cause Many populations have an infection rate of almost a hundred per cent without much morbidity directly due to the worms, and great care must be taken to view these hookworm infections in their proper perspective and not attribute either too much or too little to them In the early days several experienced investigators made serious mistakes in this direction (*e.g* Giles in Assam attributed kala azar to hookworm infection) In the absence of other obvious causes of illness and on the finding of perhaps a single egg it is often tempting to label a patient 'ancylostomiasis' but this should not be done without first carrying out a very thorough investigation to exclude other causes and finally applying the therapeutic test On the other hand light sporadic infections in some social groups in Europeans in India for example may be responsible for mild but troublesome gastro-intestinal disturbances such as continuous epigastric discomfort and they should not be ignored

Examination for ova.—It will be possible to make a diagnosis in any clinically significant infection and even a rough estimate of the hookworm load by a direct examination of a stool emulsion under the microscope but for recognizing very light (initial or residual) infections for example in testing the efficacy of a drug concentration (*e g* flotation) methods should be used

TECHNIQUE

Direct examination.—A small piece of stool is placed directly on a large microscopic slide 3 by 1½ inches a little saline sufficient to make a thin emulsion is added, and a large coverslip 1½ by ⅞ inches, is placed over it. The whole portion under the coverslip is examined with a low-power (2/3) objective and a no. 10 eye-piece Periodically it may be necessary to bring the 1/6th objective into operation to identify some special object, but the initial search for ova should be made with the low power lens. Three negative slides may be accepted as evidence that there is no clinically significant infection.

Flotation methods.—A piece of stool about the size of half a walnut is placed in a round-bottomed centrifuge tube Tap water is added and the stool emulsified The emulsion is now filtered through wet cheese-cloth (18-20 mesh) and then centrifuged at high speed for 70 seconds, the supernatant fluid is poured off fresh water added and the centrifugalization is repeated several times until the supernatant fluid is clear A small amount of 33 per cent zinc sulphate solution (specific gravity 1.180) is now added to the sediment which is broken up with a glass rod, and the tube is then filled almost to the top with zinc sulphate solution It is again centrifuged for 70 seconds. A few more drops of solution are added very carefully with a pipette to fill the tube to the brim and make a meniscus, and a coverslip is placed in contact with this meniscus ova tend to adhere to the cover-glass. This is lifted off placed face downwards on a slide and examined for ova

In the absence of a centrifuge the zinc sulphate solution can be added directly to the fæces, mixed thoroughly and allowed to stand for a few minutes, after which the floating ova are collected on a cover-glass in the way described above

Lane direct centrifugal flotation method which entail the employment of a special apparatus is dependent on the same principle it is possibly the best method for finding the last egg in a stool but the former of the methods described above falls very little short of Lane's method and i sufficiently accurate for all practical purposes

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We have adopted the principle of grouping hookworm load as follows —

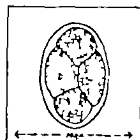
I	Light load	under 2,000 eggs per gramme
II	Moderat load	over 2,000 but un l r 10 000 eggs per gramm
III	Heavy load	over 10 000 but un ler 40 000 eggs per gramme
IV	Very heavy load	over 40,000 eggs per gramme

The last figure is equivalent to a load of 1,000 worm

After treatment the worms can be counted by collecting all the stools for 48 hours and washing them through a fine (1 mm mesh) copper sieve The adult worms will be held back by the sieve and can be counted

There are several method for estimating the number of ova but the following modification of the original Stoll method is in the writer's experience the best —

Technique—A test-tube of suitable size is mark d at the 27 c m and the 30 c.cm lev ls. Decinormal sodium hydroxid poured into the tube up to the 27 c.m lev l and portions of stool re added unt l the fluid reaches the 30 c.c level. The content of the test-t be re now poured into a bottle containing glass bead and the test-tube is washed out thoroughly with a measured 60 c.cm of N/10 sodium hydroxide which is also added to the bottle The final dilution of the stool is thu about 1 in 30 The bottle i corked and shaken thoroughly and if necessary left over-night to ensure complete disintegration of solid fæces. With a measuring pipette exactly 0 15 c cm of emulsion is placed on a large slide, and large cover-sl p is placed over t Th number of eggs on two such slid s is counted This figure multiplied by 100 gi es the numbe of eggs per gramme of stool


Figure 148 The egg of the hookworm

Other diagnostic aids —Instances have been reported in which though no ova were found in the stools adult worms were found post mortem The usual explanation is that these have all been male worms If this state of affairs is suspected the therapeutic test and careful examination of the stools for adult worms should clear up the point

The finding of an eosinophilia will naturally lead to a suspicion of some helminth infection but will be of no real diagnostic value further when the infection is a heavy one and the morbidity considerable there will usually be no eosinophilia

If the examination of the stool is delayed for any reason the ova may hatch into rhabditoid larvæ and these will have to be differentiated from rhabditoid larvæ of *Strongyloides* The most striking point of difference is the very short buccal cavity of the latter In extreme cases filariform larvæ may develop, but the differentiation of these from the filariform larvæ of *Strongyloides* presents little difficulty as the latter have a notched tail that is quite characteristic

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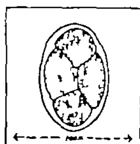


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PREVENTION

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representative groups of the populations including at least *some rough* estimation of hæmoglobin an examination of the stools preferably of the *same individuals* and an estimation of the percentage of infected persons and of the degree of their infection—a better evaluation of the latter will be obtained by classifying the population according to the number of ova they are passing (*see* p 597) than by working out an average for the whole number examined—and finally if possible, an estimation of the infectivity of the soil* in areas where most infections are thought to occur this last investigation should be made at several *different times* of the year These examinations will have to be repeated periodically to measure the success or failure of the procedure (For short descriptions of the method of stool examination *see* p 596)

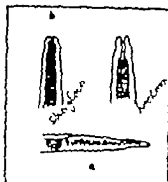


Figure 149 The anterior ends of the rhabditoid larvæ of (*a*) the hookworm and (*b*) *Strongyloides* and (*c*) tail of the filariform larva of *Strongyloides*

In order to obtain a view of the subject of prevention in proper prospective it should be *considered under two headings*, namely (I) the prevention of hookworm infection, and (II) the prevention of hookworm disease despite the fact that there will be *much overlapping* in the two aims

(I) Prevention of infection —The reader is asked to turn back to p 590 where the five essentials for hookworm infection are given we will consider the subject under each of these five headings —

(*a*) Man is the sole reservoir of infection of the two important species, so that effective anthelmintic treatment will have the double result of curing the individual and reducing the source of infection in the community

(*b*) The circumstances are such that it is seldom that anything can be *done to improve the terrain* but *where the area is a very limited one*, as in mines attempts have been made to reduce its suitability as a medium of infection by treatment with such substances as common salt.

(*c*) The proper disposal of human fæces by the installation of sanitary latrines and the encouragement—or the enforcement—of their use by the whole population is the crux of the whole hookworm problem and where this is possible all other preventive measures become subsidiary This is not the place to discuss methods which will naturally vary with the conditions In some places in India the bored hole latrine has been a very useful solution as the individual nature of this system obviates the

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* *Estimation of larvæ in soil.*—This is most easily accomplished by the Baermann technique, which depends on the fact that larvæ will migrate out of soil into warm water that comes in contact with the lower surface of this soil The technique is described by Craig and Faust (1943) as follows —

The simple apparatus used consists of a glass filter funnel of 15 to 23 cm. diameter (preferably ribbed) placed in a convenient rack or ring-stand, and connected *at its lower* end with a short rubber tube provided with a pinch-cock The soil sample to be tested is placed in a little basket made of 1 mm mesh bronze screening lined with cheese cloth. Lukewarm water is placed in the funnel, and its height is so adjusted that the lower level of the soil will come in contact with the upper level of the water when the wire basket is set into the funnel. Within ten to fifteen minutes, nematode larvæ in positive soils may be observed migrating down the stem of the funnel The maximum yield takes place within the first hour after which the pinch-cock should be opened, about 25 to 50 c.c. of water drawn off into a test-tube the suspension centrifugalized the supernatant fluid pipetted off immediately and the sediment poured on to a fæcal slide for examination. The examiner needs considerable skill and experience to differentiate hookworm and *Strongyloides* larvæ from nematodes free-living in the soil.

prejudices that are entertained regarding the communal latrine It is of the utmost importance that any scheme that is introduced should be easily workable and suited to the special circumstances it must not be liable to break down as an unsatisfactory latrine will do more harm than good This aspect of prevention is so important that it must always be remembered that whatever other measures are taken the only enduring solution will be proper disposal of human excreta the source of infection and a beginning must be made to this end

Education and propaganda will play an important part in the prevention scheme as not only has understanding to be imparted interest aroused and ingrained habit broken, but quite often active prejudice has to be overcome

Where human excreta are used for manure either septic tank treatment for a considerable time at least three months in a temperate climate or six weeks in a tropical one or some other means of sterilization must be employed *e g* the addition of lime to a dilution of 1 in 500 or mixture with litter to make a form of compost and burial in the earth will raise the temperature sufficiently to destroy the egg and larvæ But this particular problem is a difficult one and has not yet been satisfactorily solved

(*d*) Climatic conditions are matters outside human control

(*e*) The wearing of good boots or shoes will decrease the chance of infection but not stop it completely Unless this is an entirely foreign custom amongst the people the wearing of boots or shoes should be urged Propaganda will again find an important place here

(II) Prevention of hookworm disease—It is again necessary to recapitulate Certain facts must be remembered —

(i) Hookworms do not undergo any multiplication within the body of the host so that without reinfection there will be no increase in their number but in fact a relatively rapid reduction (placed at 70 per cent in the first year by some observers) will occur If the infection is not to die out it will have to be repeatedly replenished We thus have the equation —

$$\text{hookworm load} = \frac{\text{the rate of acquisition of infection}}{\text{the rate of worm loss}}$$

(ii) The hookworm load at any particular moment will vary from one worm to several thousand and similarly the infection may be either sub-clinical or clinical however the relation between these two facts is not a simple and direct one but morbidity is dependent also on the tolerance of the host or in other words

$$\text{morbidity} = \frac{\text{hookworm load}}{\text{host tolerance}}$$

(iii) Host tolerance is dependent on certain fixed factors, such as age and race but it is also influenced considerably by a variable factor the diet of the host.

The eventual aim of prevention is the reduction of hookworm morbidity in the population It will be seen from the above equation that this can be done by

(*a*) reducing the hookworm load, or
(*b*) increasing the tolerance of the hosts

The hookworm load can be reduced by

(*c*) decreasing the rate of acquisition of infection or
(*d*) increasing the rate of worm loss

We can achieve (*c*) mainly by improving environmental hygiene (*vide supra*) but there is some evidence mostly on analogy with camp infection that diet affects the rate of effective infection and (*d*) will be achieved by anthelmintics and to some extent possibly also by suitable

Referring to the number of worms that actually reach the bowel.

dietary The only practicable measure for achieving (b), increase in tolerance is also by dietary improvement

Thus to summarize hookworm morbidity can be reduced by —

(i) Improvement in environmental hygiene (*sensu lato*)

(ii) Anthelmintic treatment

(iii) *Improvement in diet*

It must be quite obvious that if the rate of the acquisition of infection is sufficiently decreased by sanitary improvement or the rate of worm loss is sufficiently increased by mass treatment, or if both effects are brought about the degree of infection of the population will decline, and average hookworm load will decrease and eventually fall below the morbidity level, if in addition the diet of the population is improved this end will be achieved at an earlier date In this way the morbidity in the population may be reduced without achieving the ideal of a perfect sanitary system which in most cases will be impossible or the complete deworming of the *community which in most cases will be* impracticable. The great disadvantage of this method of approach is that continued vigilance to ensure that there is no dangerous increase in the hookworm infection in the population and usually periodic retreatment will be necessary

Policy —There have in the past been two schools of thought. The more realistic school demanded a reduction in the hookworm morbidity on the lines indicated in the last paragraph success being measured by the reduction of this morbidity in the community The idealistic school considered that the aim should be the removal of the last hookworm failure to achieve this being measured in terms of the number of infected persons *left in the population*

We will consider the latter first It is impossible to criticize the ideal but how far is the aim practicable? To achieve complete success not only the cases with symptoms but every member of the population who shows any hookworm infection must be treated (if he will consent) To ensure the removal of all the worms even by the most efficient method, at least three treatments will be required in a large number of cases and an *elaborate method of stool* examination will be necessary to check the results Further this whole process will usually have to be repeated at monthly intervals for a period of four months to catch all the fresh worms—those migrating in the tissues and those acquired from larvæ surviving in the soil since the first mass treatment—before they can produce any eggs. Even then a few worms may escape and should complete success be achieved a casual visitor might reinfect the ground and start the whole infection cycle again There might be occasions when in an *isolated* community such a measure would be both practicable and advisable, but, as a general rule complete success would be so improbable that it would be *scarcely* worth attempting.

The policy of the realistic school is the one now generally adopted Complete treatment of the whole community is not usually attempted, but treatment is concentrated on the members of the families or of the habitation groups in which any cases of hookworm *disease* are found one course of anthelmintic treatment is given to each member and medical treatment for the anæmia plus a second course of anthelmintics if necessary *to those* with clinical evidence of the disease The most favourable time for giving such a course of treatment is during the period—when there is one—in which transmission does not occur *e g* in the southern states of America the temperature prevents transmission between November and March.

By this modification of the mass treatment programme much time-consuming laboratory work is saved and the number of treatments given

is reduced very considerably although it may be advisable to repeat the treatment every few years. It has been found that, if this procedure is combined with the provision of latrines and the dissemination of propaganda regarding their proper use a steady decline in morbidity will take place year by year

In conclusion it must be remembered that none of the measures mentioned above can be put into effective operation without explaining to the people the cause of the disease and the necessity for their whole hearted co-operation so that to the measures summarized on p 600 must be added

(ii) Education and propaganda

TREATMENT

This must be considered under the two major headings (I) treatment of the parenteral infection and (II) treatment of the intestinal infection and the latter can be divided into (*a*) specific treatment and (*b*) general treatment.

I Of the parenteral infection.—Except that in the case of *creeping eruption* the larvæ of *Ancylostoma braziliense* may be destroyed in the skin by the application of carbon dioxide snow ('dry ice') or by the ethyl chloride spray no method of affecting the larvæ before they reach the intestinal canal is known Antiseptic lotions and dressings should be applied to the skin lesions to obviate or cure secondary infection

II Of the intestinal infection.—(*a*) Specific

Historical.—Prior to about 1917 chloroform beta-naphthol and thymol were the principal drugs used of these thymol was undoubtedly the best. A dose of sixty grains was given to an adult usually in divided doses there were often unpleasant bye-effects which might be serious if alcohol were taken Three treatments at least were usually required to reduce the worm load to a negligible level Thymol is a relatively expensive drug, and, as cheaper safer and more effective drugs have since been introduced, it only deserves mention in an historical section

Chloroform and oil of eucalyptus was the standard treatment for this and other helminth infection in the early days of the century and deserves honourable mention whereas beta-naphthol is quite useless in safe doses and it is difficult to see why it was ever advocated

In 1915 Victor Heiser used oil of chenopodium in over 10,000 cases with success and no bad results This drug, which had been first suggested by Schüffner and Vervoort in 1900 depends for its efficacy and its toxicity on its ascaridole content this unfortunately varied in different samples, so that in different workers hands results were not uniform and dangerous bye-effects, including some deaths resulted in a few cases. It is now a standardised pharmacopœial drug and is very useful in mixed ascaris and hookworm infections, when it is combined with carbon tetrachloride or tetrachlorethylene but given alone for hookworm infection its effective dose (3 c cm for adults) is dangerously near its toxic dose, so that it has been superseded except for mixed infections

In 1922 Leach used carbon tetrachloride in man a drug that had been used successfully in dogs by Hall and it was later used in hundreds of thousands of human cases without apparently causing any ill-effects At this time it was by far the most effective drug. It was shown experimentally however, to have a very damaging effect on the liver cells and several cases where this followed therapeutic doses were reported. Further if any alcohol was taken immediately before or shortly after the carbon tetrachloride the liver damage was likely to be extensive and several groups of fatalities amongst subjects of mass treatment were reported Such incidents had a very serious effect on treatment campaigns and this drug fell into disfavour for this purpose, although it was still used extensively and still is for the treatment of such patients under hospital discipline A safe dose for an adult is 3 c.cm and for children 0.2 c.cm. for each year of age It is given in the same way as tetrachlorethylene (*vide infra*) but special emphasis must be placed on the dangers of taking alcohol, before or after

In 1925 tetrachlorethylene was introduced. It appeared too late to be used in the extensive Rockefeller Foundation treatment campaigns so that it was slow in receiving the recognition that it deserves However it has now been used in

Epidemiology.—The conditions which favour this infection are roughly those which *favour hookworm* infection, although there are obviously certain differences in the factors concerned, for there is certainly no parallelism in the *intensity of the infections* by these two worms in different parts of the endemic areas.

There is a *distinct male predominance* amongst the persons infected, and the age groups with the heaviest infection rates are in the second decade.

The incidence is *often high in institutions* such as mental hospitals.

ÆTIOLOGY

The causal organism.—The stages through which the worm passes are as follows —

The egg.—This is fully embryonated on discharge from the uterus it is deposited in the tissues in the parasitic phase and is seldom seen except in experimental infections It has a thin transparent shell, is ovoid in shape and measures about 54 by 32 microns

The rhabditoid larva.—This develops from the egg in the tissues reaches the lumen of the gut, and is passed usually in this form, in the fæces. It is about 250 microns in length and can be distinguished from the hook worm larva by its shallow buccal cavity

The filariform larva.—This develops from the rhabditoid larva usually outside the body, but also in other instances within the intestinal canal. It is a long (about 1 mm) fine larva with a long œsophagus and a distinctly notched tail Occasionally dwarf filariform larvæ develop from the rhabditoid larvæ in the intestinal canal.

The adult.—There is a considerable difference between the free-living female which is short and thick, about 1 000 by 60 microns and the parasitic female which is much longer (about 2.2 mm.) and finer The male is shorter, about 750 microns has a ventrally curved tail and is very similar in the free-living and parasitic phases.

The life cycles.—The filariform larva is the infective stage. The larvæ enter the skin of man in the same way as the ancylostoma larvæ but also through the buccal or pharyngeal mucous membrane reach the

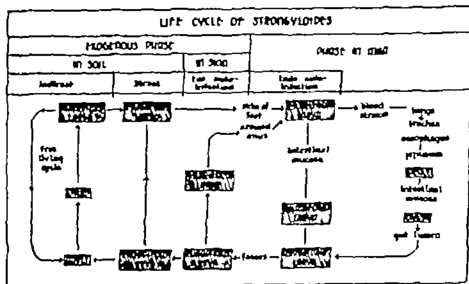


Figure 150

lungs *via* the blood stream and penetrate into the alveoli They may develop into adults here but otherwise they ascend *via* the bronchi and trachea to the epiglottis *and pass down the œsophagus into the intestinal*

anal, and the females penetrate the mucosa of the duodenum or jejunum (usually) where they deposit their eggs. Occasionally females penetrate and oviposit in the bronchial or tracheal mucosa The female lays on an average 50 eggs a day Within the mucosa the eggs develop into rhabditoid larvæ which work their way out into the bowel lumen and pass out with the fæces The whole journey takes about a month These larvæ feed on organic matter in the soil

One of two things will now happen —

If the larvæ find themselves in a sub-optimal medium they develop into non feeding filariform larvæ which are the infecting forms they enter another host and the direct parasitic cycle is complete

Or if conditions are optimal then the rhabditoid larvæ feed pass *through one moult, feed again, and develop into free-living adults* these mate the female lays eggs which develop into rhabditoid larvæ in the soil and the free-living cycle is repeated probably an infinite number of times as long as conditions remain favourable but, when they cease to be so the rhabditoid larvæ develop into filariform larvæ which though they will survive as such in the soil for many months are immediately infective and capable of entering another human host to complete the indirect parasitic cycle

This does not exhaust the possible cycles but we must go back to the rhabditoid larvæ in the intestinal lumen. Instead of passing on to the soil with the stool these may adhere to the skin or the hairs around the anus and there develop into filariform larvæ which immediately re-enter the skin of the host and recommence the cycle Or the rhabditoid larvæ may not pass out of the intestinal canal at all but develop into filariform larvæ usually the dwarf forms referred to above and penetrate the bowel wall to reach the blood and recommence their cycle The former of these last two cycles was described by Fulleborn and called by him auto-infection and the latter by Faust who called it hyperinfection

Thus to summarize, there are four parasitic cycles (*a*) endo-auto-infection (Faust's hyperinfection) (*b*) exo-auto infection (Fulleborn's auto-infection) (*c*) direct (comparable to that of the hookworm) and (*d*) indirect in which the free-living cycle is interposed (*see* figure 150)

Discussion —The practical significance of the auto-infection cycles is that an individual can apparently retain the infection almost indefinitely without renewing it from outside The auto-infection cycles are nowhere common they are more important in temperate climates where both conditions for the survival and opportunities for the re-entry of the parasite are unfavourable but they are believed not to be confined to these climates as was at one time supposed The free-living cycle makes it possible for sporadic infection of man to occur without recent contamination of the soil and should theoretically at least make prevention more difficult. Another point of difference between strongyloidiasis and ancylostomiasis is that oral infection is *apparently achieved more easily in the former so that* an infection can be initiated under conditions which would preclude entry through the skin of the feet or hands

Contributory factors in determining morbidity —There is considerable evidence that diet is a very important factor in determining pathogenicity in this infection both in the population and in the individual

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The word hyperinfection seems a most unfortunate choice for this cycle The word is well established in medical language as meaning a very intense infection This cycle is certainly auto-infection, but if it is desirable to differentiate it from Fülleborn's auto-infection—and from a practical point of view it is questionable whether it is necessary—then the word 'exo-auto-infection might be used for the Fülleborn cycle and endo-auto-infection for the Faust cycle

In children who are malnourished and/or debilitated as a result of dise the adult and larval worms appear to be able to burrow much more dee into their tissues and cause more serious damage.

PATHOLOGY AND SYMPTOMATOLOGY

As in the case of hookworm infection this worm produces pathoge lesions commonly at three points on its course (a) in the skin at the po of entry (b) in the lungs, and (c) in the intestinal mucosa and rarely the bronchi and trachea.

(a) **The skin** —Here the filariform larvæ may produce petech hæmorrhages at their points of entry The site later becomes very ir tating and there may be a localized œdema

(b) **The respiratory tract.**—Hæmorrhages may be caused in the lu and these may be associated with a cellular exudate into the alveoli Th frequently causes a cough during which blood stained sputum contami larvæ may be brought up, and after heavy infections an atypical pneumor may occur Occasionally, *the worms mature in the lungs and invade t* columnar epithelium of the bronchi and trachea causing a local exuda The respiratory lesions and symptoms are likely to be greater in th infection than in ancylostomiasis.

(c) **The intestinal tract.**—The adult females invade the mucosa deep as the muscularis mucosæ and cause desquamation and occasional sloughing of the mucous membrane with abdominal discomfort or pai sometimes a frank dysentery *but more usually a profuse watery diarrhœ* or diarrhœa alternating with constipation loss of weight and indigestio The infection is often associated with insomnia restlessness and depressio

The blood picture —There is usually a slight leucocytosis, with a 8 to 10 per cent eosinophilia at first and later a leucopenia There ma be some slight degree of anæmia usually of the macrocytic nutritiona type

Diagnosis —This can be made by finding the larvæ in the stool Concentration of the stool will facilitate this The larvæ appear in th stools intermittently and therefore no importance should be attached to single or even several negative findings Further the larvæ may di and be digested during their relatively long journey down the intestina canal thus, *in a case in which the infection is strongly suspected*, som workers recommend that a duodenal aspiration should be done. Or th larvæ may be coughed up in the sputum.

The larvæ have to be differentiated from the hookworm larvæ, th main point of difference is the shallow buccal cavity in the strongyloide rhabditoid larva and the notched tail in the filariform larva (*vide supra*)

PREVENTION

The main measures to be adopted are those employed against hook worm infection (*quod vide*) In addition, the existence of this infectior in an institution suggests the need for all round improvement in sanita tion a higher standard of personal cleanliness and greater care in the preparation of food Uncooked vegetables and contaminated water supplies are important sources of infection that can usually be obviated.

Improvement in the diet of an infected population or individual will help to prevent the more serious results of infection.

TREATMENT

This has been very disappointing as none of the anthelmintics that have been so successful in the treatment of ancylostomiasis have proved of any value in this infection Gentian violet is considered the

only specific but this has not been successful in the hands of all workers, in some cases this was possibly because they did not adopt the right technique but there is evidence of a variable resistance to treatment Experiments have shown this drug will penetrate at least as far as the muscularis mucosæ.

The most efficient method of administration is by intubation of the duodenum, into which 25 c cm of a 1 per cent dilution of *medical* gentian violet is given in one dose this can be repeated after a few weeks if the infection is not eradicated

The alternative simpler and almost equally efficacious method is to give gentian violet in the form of 1½ hour enteric-coated tablets (Eli Lilly's Enseals) The ordinary dosage is one grain (two tablets) three times daily one hour before meals for 17 days an approximate total of 50 grains adult doses are given to older children weighing over 100 pounds one grain twice daily to children between 75 to 100 pounds and half a grain thrice daily to those between 50 and 75 pounds

Dr J S D'Antoni (personal communication) recommends a concentrated 4-day treatment in which he gives two ½-grain tablets thrice daily before meals on the first day three on the second day four on the third and five on the fourth a total of 21 grains

For parenteral infections *e g* lung up to 25 c cm. of 0.5 per cent aqueous solution of gentian violet given intravenously on alternate days for five doses is recommended

This drug may cause nausea and abdominal discomfort in certain individuals but as it is the only drug known to be of any value it should be persevered with if possible After administration of an efficient course of gentian violet, larvæ may be found in the stools for several weeks before finally disappearing which seems to indicate that the drug does not destroy the eggs

TRICHOSTRONGYLIASIS

Several species of the genus *Trichostrongylus* parasitize man but most of them are the normal parasites of other mammals, and only incidentally infect man. One species *Trichostrongylus orientalis* has been found in man more than twenty times by one observer (Jimbo 1914) and is believed to be mainly if not entirely confined to man

These worms occur in many countries in the world, from the tropics to Siberia and their life cycle is apparently very similar to that of the ancylostomes so that they are likely to be found in the same individuals. However they also gain entrance by the ingestion of uncooked vegetables

The adults are found with their heads buried in the mucous membrane of the small intestine They can suck blood and there is usually hyperæmia surrounding their points of puncture which suggests that they may inject some toxic substance and/or allow the entry of septic organisms In cases with heavy infections emaciation and anæmia have been attributed to the worms but they are evidently not more than low grade pathogens and their importance in medicine rests almost entirely on the fact that it is easy for the unexperienced to mistake their eggs for those of the hookworm.

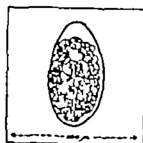


Figure 151 The egg of *Trichostrongylus*

Further they are very resistant to treatment and Maplestone (1941) states that several patients sent to him as suffering from treatment resistant hookworm infections have turned out to be infected with *Trichostrongylus* However the usual course

of treatment for hookworm infection (*quod vide*) is the only treatment known to be at all effective.

Identification of the ova.—Compared with hookworm ova the ova are larger and more characteristically egg shaped, that is, pointed at one end, and there is a much larger clear area usually at both poles. Maplestone (*loc. cit.*) gives the average measurements as 89 by 48 microns compared with 62 by 41 microns for hookworm eggs.

The ova usually hatch within twenty four hours under favourable conditions, producing pseudo-rhabditoid larvæ that differ from hookworm larvæ mainly in that the musculature of the œsophagus is not well developed, and, although present, the posterior bulbous portion is not clearly seen as in the true rhabditoid larva of the hookworm.

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TAPEWORM INFECTIONS*

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Tænia solium Linnaeus 1758 the pig tapeworm and

* For hydatid disease see p 606.

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Diphyllobothrium latum (Linnaeus 1758) Lube 1910 the
tapeworm.

and two dwarf tapeworms —

Hymenolepis nana (v Siebold 1852) Blanchard 1891

Hymenolepis diminuta (Rudolphi 1819) Blanchard, 1891

LARGE TAPEWORMS

Geographical distribution —None of these infections is tropical in its distribution As however they depend for their distribution upon the eating habits of the people in the various countries and as the control of meat supplies is more lax in tropical countries the meat-eating sojourner is perhaps more likely to contract an infection with either the pig or the beef tapeworm in a tropical country than in the United States or in any of the western European countries In eastern Europe the pig tapeworm especially is relatively common.

The fish tapeworm on the other hand is rare in the tropics and occurs in the Baltic countries northern Italy and Switzerland in the Danube delta in Palestine in Siberia Manchuria and Japan in some places in the northern states of America and in Canada and sporadically elsewhere. In the last-named countries the foci of infection are mostly on the shores of the great lakes where the infection was probably introduced by Scandinavian immigrants but recently a focus has been found in Florida

ÆTIOLOGY

The parasites —The tapeworms are flat hermaphroditic worms consisting of (*i*) a scolex the so-called head which is an attachment organ (*ii*) the neck which is narrow and formed by a number of undifferentiated proglottids (*iii*) a short section of differentiated but immature proglottids or segments in which the male and female sex organs are present (*iv*) a long section of mature proglottids and finally (*v*) the gravid proglottids These worms have no digestive tracts but absorb nutrition from their environment in the gastro-intestinal tract of their hosts The life cycles of the different species vary so much that it will be necessary to describe them separately

Life cycles

Tænia saginata.—Man is the only important definitive host he passes the proglottids in his fæces and when these disintegrate the ova which are spherical 30 to 40 microns in diameter have a thick shell and contain an onchosphere with three pairs of hooks are set free These are ingested by cattle in whose gut (duodenum) onchospheres emerge and penetrate the bowel mucous membrane reach the systemic circulation and are filtered out in the muscles Here they develop into cysticerci in about 60 days These cysticerci, which are white oval bodies 7 to 10 by 4 to 6 microns are the infective form for man who ingests them in un or under cooked meat From the cysticerci the worm develops attaches itself to the small intestinal mucosa and proceeds to grow into a mature worm measuring from 4 to 10 metres with as many as 2 000 segments in about three months. Gravid proglottids now begin to drop off one by one pass out of the anal orifice under their own power or in the fæces and the cycle is complete

Tænia solium—The cycle of this tapeworm is similar to the above with the pig replacing cattle as the usual intermediate host. However an alternative route is provided by the fact that man may also function as

an intermediate host If the eggs are ingested by man from another host by oral reinfection from the proglottids of his own adult worm or by endo-auto infection brought about by reverse peristalsis the proglottids or eggs reach the stomach where the covering is digested off and the onchospheres emerge penetrate the intestinal mucosa and, reaching almost any part of the body via the blood develop into cysticerci (see figure 1 2) From this point the cycle could be continued only by cannibalism

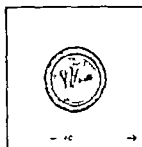


Figure 152 The egg of Tænia

Diphyllobothrium latum.—There are many definitive hosts of this worm other than man—the domestic pig the domestic dog and cat and other canines and felines walruses seals sea lions minks and bears The eggs which are golden brown in colour ovoid 45 by 70 microns contain immature larvæ within a thin shell and have an opening at one pole covered by a cap, are passed in the fæces In water these mature within 15 days and the embryos (coracidia) emerge these are ciliated and swim freely in the water up to 12 hours after which they would die if they were not ingested by a copepod (crustacean) of certain species of the genera Diaptomus and Cyclops They develop in these for two to three weeks and when the crustacean is swallowed by fish these embryos develop into plerocercoid larvæ long white larvæ measuring up to 6 millimetres in the flesh (muscle) of the fish The small fish that eat the crustaceans are later eaten by larger fish such as pike perch trout and other fish commonly eaten by man (and other definitive hosts) and in the human intestine these larvæ develop into adult tapeworms in about six weeks This species grows to a length of 10 metres or more and may have as many as 3,000 proglottids The eggs are evacuated into the intestinal canal from the mature proglottids which do not separate as in the case of the other tapeworms but atrophy after they have discharged their full egg load These worms may produce as many as a million eggs a day but they usually evacuate their eggs periodically about every third day for about a month The eggs are passed out with the fæces and the cycle is complete

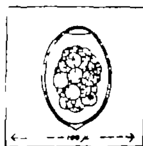


Figure 153 The egg of *D phyllobothrium latum*

EPIDEMIOLOGY

These infections occur amongst meat and fish-eating persons in many countries but are particularly common amongst groups who eat their food raw or only lightly cooked and in countries where pigs have easy access to human fæces which they will readily eat or cattle graze in pastures which are frequently contaminated by or deliberately manured with human excreta.

A number of cysticercus infections in British soldiers who have been stationed in India have been reported This is surprising as in only very few indigenous population groups is *Tænia solium* infection common in that country which has a large Mohammedan population to whom the pig is *tabu* Most of the balance of the indigenous population consists of Hindus to whom the cow is sacred and who for the most part are strict vegetarians

The fish tapeworm infection appears to be extending in the United States several fresh endemic foci have been identified and infected fish is sometimes sent to market in distant towns

PATHOLOGY AND SYMPTOMATOLOGY

In none of these infections do the adult worms or the encysted larvæ ordinarily invade the host's tissues but they deflect a certain amount of the host's nutriment to their own use, and secrete substances which may act as toxins or allergins Rare instances of the scolices having penetrated the intestinal wall and caused peritonitis have been reported. And finally the cysticerci of *T solium* may develop in man, as they do in the usual intermediate host, in any tissue or organ of the body As the pathogenesis and symptoms produced by each of the two stages of the worm are of an entirely different order from that produced by the other it will be advisable to describe them separately

The adult worms.—The symptoms produced are irregular and ill-defined Loss of weight indigestion and general abdominal discomfort and in allergic individuals periodic diarrhœa may occur All somatic symptoms may be absent, especially in *T saginata* infection, but the host may be reduced to a state of neurasthenia by knowledge of the presence of the worm and by the embarrassment caused by the emerging segments, which may appear at unexpected moments on the host's stockings or shoes. In *D latum* infection, however there is in certain cases evidence of some intoxication produced by the metabolites of the worm. A macrocytic anæmia of the pernicious anæmia type has for many decades been associated with this infection Although the work of Birkeland (1932) seemed to cast doubts on the causal relationship between the infection and the pernicious anæmia that is very prevalent among Finnish nationals, more recent work seems to support the suggestion that the worm metabolites which are of the nature of unsaturated fatty acids are capable of producing anæmia (Wardle and Green 1941) Anæmia has not been reported in Canadian and north American cases

The cysticerci of T solium.—The onchospheres having reached the blood stream migrate into the tissues in any part of the body but appear to have a preference for the brain the muscles and the subcutaneous tissues. Here they give rise to a tissue reaction and are eventually surrounded by a fibrous capsule of host origin Within this rigid host capsule the cysticercus continues to develop the parasitic wall of the cyst becomes folded upon itself and in some cases produces a relatively large 0.5 to 1 centimetre, racemose cystic growth There is apparently a stage at which a balance between host and parasite is reached and no further development takes place for several years but when the parasite dies this symbiosis is disturbed the capsule becomes permeable and fluid enters and toxin escapes so that there is renewed tissue reaction and an increase in the size of the parasitic mass at least temporarily Later there is calcification or the foreign body is partly or completely removed. The life of the cysticerci is probably very variable but it is probable that they live for at least three years and after their death at least another three years elapse before they become calcified

The symptoms depend on the site in which the cysticerci are located and of course on the number present. A heavy invasion may be associated with pyrexia other general symptoms of a toxæmic nature and pressure symptoms if vital tissue is involved. Generally however the symptoms are postponed until the worm dies when further pressure and toxæmic symptoms may appear The symptoms associated with the foreign body effect of the cysticercus in the tissues frequently do not develop until the worm is dead and calcification has occurred

The sites where they are most usually reported are (*i*) in the subcutaneous tissues where they form lumps that are clinically recognized, (*ii*) in the brain where they produce a number of symptoms from mild mental

changes such as deterioration of memory to Jacksonian epilepsy and total mental degeneration and are recognized by x ray examination, (iii) in the eyes where they may actually be seen in the anterior or posterior chamber and (iv) in other tissues such as the muscles where they may be recognized accidentally during x ray examinations or at post mortem

DIAGNOSIS

In tænia infections this will usually depend in the finding of the proglottids in the stools or on their presence being reported by patients, and in *D latum* infection by the finding of the eggs in the stools

In *T solium* and *T saginata* infection eggs will occasionally be found in the stool but this finding must not be expected The eggs are practically identical and for differentiation one must rely on examination of the mature or gravid proglottids This can be done by flattening them out on a slide placing a coverslip over them examining the uterus and counting its *primary* lateral branches in *T solium* there are 7 to 13 primary branches and in *T saginata* 15 to 20

After unsuccessful treatment that leaves the scolex *in situ* proglottids will usually reappear in the stools within three months

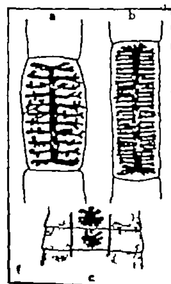


Figure 154 Proglottids of (a) *Tænia solium* (b) *Tænia saginata*. (c) *Diphyllobothrium latum*

On the other hand the eggs of *D latum* may be found in the stools but a number of examinations will have to be carried out before a negative diagnosis can be made as they are extruded by the worm intermittently In this infection proglottids are not usually found in the stools in an untreated case they are quite distinct from the other two being much shorter and broader and having an almost stellate uterus

The presence of cysticerci may be diagnosed by the palpation and/or removal of the tumours in the subcutaneous tissues or muscles by the symptoms they produce when they occur in vital tissues or by x ray examination. The x ray examination requires special experience the exposure should be that given for bone visualization with a slight under exposure The opacity may be produced by a calcified scolex one millimetre in diameter or by a fully developed cysticercus as large as two centimetres in length. It will seldom be worth taking a skiagram within six years of the probable time of infection

It has been said that whenever epileptic fits occur in an adult without a history of injury or a family history of epilepsy cysticercosis should always be suspected

PREVENTION

If the beef pork and fish are properly cooked the cysticerci will be destroyed (65.5 C is lethal) and direct personal prophylaxis achieved.

As a measure of general prophylaxis in most countries meat is inspected. In the United States two-thirds of the beef that is consumed by the public is inspected. In 1930 0.37 per cent of carcasses were found infected and were condemned the figure has improved in recent years Pork is similarly inspected and measly pork discarded.

It is possible to go one stage further back in the matter of prophylaxis

PATHOLOGY AND SYMPTOMATOLOGY

In none of these infections do the adult worms or the encysted larvæ ordinarily invade the host's tissues but they deflect a certain amount of the host's nutriment to their own use and secrete substances which may act as toxins or allergins. Rare instances of the scolices having penetrated the intestinal wall and caused peritonitis have been reported. And finally the cysticerci of *T solium* may develop in man as they do in the usual intermediate host in any tissue or organ of the body As the pathogenesis and symptoms produced by each of the two stages of the worm are of an entirely different order from that produced by the other it will be advisable to describe them separately

The adult worms.—The symptoms produced are irregular and ill-defined. Loss of weight indigestion and general abdominal discomfort and in allergic individuals periodic diarrhœa may occur All somatic symptoms may be absent especially in *T saginata* infection but the host may be reduced to a state of neurasthenia by knowledge of the presence of the worm, and by the embarrassment caused by the emerging segments, which may appear at unexpected moments on the host's stockings or shoes. In *D latum* infection however there is in certain cases evidence of some intoxication produced by the metabolites of the worm. A macrocytic anæmia of the pernicious anæmia type has for many decades been associated with this infection Although the work of Birkeland (1932) seemed to cast doubts on the causal relationship between the infection and the pernicious anæmia that is very prevalent among Finnish nationals, more recent work seems to support the suggestion that the worm metabolites which are of the nature of unsaturated fatty acids are capable of producing anæmia (Wardle and Green 1941) Anæmia has not been reported in Canadian and north American cases

The cysticerci of T solium—The onchospheres, having reached the blood stream migrate into the tissues in any part of the body but appear to have a preference for the brain the muscles and the subcutaneous tissues Here they give rise to a tissue reaction and are eventually surrounded by a fibrous capsule of host origin. Within this rigid host capsule the cysticercus continues to develop the parasitic wall of the cyst becomes folded upon itself and in some cases produces a relatively large 0.5 to 1 centimetre, racemose cystic growth. There is apparently a stage at which a balance between host and parasite is reached and no further development takes place for several years but when the parasite dies, this symbiosis is disturbed, the capsule becomes permeable and fluid enters and toxin escapes so that there is renewed tissue reaction and an increase in the size of the parasitic mass at least temporarily Later there is calcification or the foreign body is partly or completely removed The life of the cysticerci is probably very variable but it is probable that they live for at least three years and after their death at least another three years elapse before they become calcified

The symptoms depend on the site in which the cysticerci are located and of course on the number present. A heavy invasion may be associated with pyrexia other general symptoms of a toxæmic nature, and pressure symptoms if vital tissue is involved. Generally however the symptoms are postponed until the worm dies when further pressure and toxæmic symptoms may appear The symptoms associated with the foreign-body effect of the cysticercus in the tissues frequently do not *develop* until the worm is dead and calcification has occurred

The sites where they are most usually reported are (*i*) in the subcutaneous tissues where they form lumps that are clinically recognized, (*ii*) in the brain where they produce a number of symptoms from mild mental

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DIAGNOSIS

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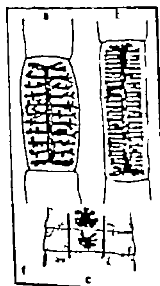


Figure 154 Proglottids of (a) *Taenia solium* (b) *Taenia saginata* (c) *Diphyllobothrium latum*

... may ... X-ray examination ... the exposure ... visualization with ... opacity may be ... one millimetre in d... developed ... as large ... metres in length. It ... taking a skiagram ... probable time of infection.

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It is possible to go one stage further back in the matter of prophylax...

and to prevent cattle from grazing on pasture contaminated with human fæces or pigs from eating human fæces Regulations to achieve this will be difficult to enforce but if meat and pork are inspected frequently and when found infected condemned and the cause of their meat becoming infected is explained to farmers the economic aspect will probably appeal to the cattle and pig raisers in the sanitarily advanced western countries and they will take the necessary steps However in eastern Europe, and in Asia where pigs and cattle are allowed to roam freely the prevention will be much more difficult.

In the case of *D latum* though there are many other definitive hosts man is believed to be the most important and the prevention of the sewage contamination of water where edible fish are caught will be an effective preventive measure

Cysticercosis cellulosæ is prevented by the immediate and thorough *treatment of all infected individuals and by observation of rigid personal* hygiene especially by those who know that they are infected. In certain circumstances isolation of the infected individual would be justifiable

TREATMENT

Male fern has been the specific for this infection for many years but some improvement has been effected recently in the preparation, the standardization and the method of administration of this drug.

An unopened bottle of the oleo-resin of *Aspidium filix mas*, or better still gelatine capsules containing 10 or 20 minims each of this drug are obtained The patient is given two ounces of saturated sodium sulphate solution at night and next morning on an empty stomach at 7 00–7.30 and again at 8.00 a.m. (or earlier if convenient) one 20-minim capsule (or two 10-minim capsules) that is a total dose of 60 minims. Two hours later a second saline purge is given and food is withheld until the patient *has passed a copious stool, which will contain the whole or most of the* worm.

The dose for young children is a total of two minims for each year of *apparent* age For children of over 100 pounds in weight 25 minims, for children of 150 pounds *and under-sized adults 45 minims and for children* over 170 pounds the full adult dose of 60 minims is given this total dose is divided into three equal parts each of which is given in a teaspoonful of sugar

This dosage will effect a cure in about 80 per cent of cases. If a patient is in hospital the stools for the next 48 hours should be kept screened and the debris examined for the scolex. If this is not present the treatment may be repeated in a week. On the other hand if the patient is at home it is a mistake *to insist* on his keeping and searching his stools as the procedure is very distasteful and is not likely to be done effectively If he is not cured he will know in due course in either of the *Tænia* infections if the scolex is not removed, proglottids will be passed again in two to three months time and in the case of the fish tapeworm there will be a return of eggs to the stools within five or six weeks

A method of treatment that is undoubtedly very satisfactory from the point of view of the physician is that practised by Dr J S D Antoni of the Tulane School After a preliminary saline purge he gives by duodenal intubation the following mixture —

Oleo-resin of male fern	1 drachm
Saturated solution of sodium sulphate	1 ounce
Mucilage of acacia	1
Water	2 ounces

No further medication is necessary and within an hour the whole worm usually intact will be passed One hundred per cent success can be expected

Of the other drugs carbon tetrachloride is the best and after this comes tetrachlorethylene the latter is safer for persons not under hospital discipline as the taking of alcohol does not have to be prohibited The dosage is the same as that given in the treatment of hookworm infection (*quod vide*) Mukerji and Maplestone (1913) obtained an 80 per cent cure rate with the former and 54 per cent with the latter These drugs are less satisfactory from the point of view of the helminthologist because the worms are often disintegrated when passed but they are cheaper easier to obtain less unpleasant to take and probably safer than oleoresin of male fern It seems very probable that by intubation they would be as efficacious as male fern by this route

It may be necessary to give symptomatic treatment also Any anæmia associated with *D latum* infection must be investigated from a hæmatological point of view and treated as indicated It is usually a macrocytic type of anæmia for which marmite (vegex) given by mouth and liver extract given either by mouth or parenterally will be indicated

Cysticercosis cellulosæ —No specific treatment appears to have any beneficial effect on the pathogenesis This is to be expected as most of the pathological changes are associated with the death of the worm Surgical removal is practicable in certain circumstances

Prognosis —In infections by the adult tæniæ the prognosis is excellent but in *T solium* infection the danger of auto-infection must be explained to the patient In established cysticercal infections however the prognosis must always be guarded as localization in the brain is very common and may not become evident for many years

Generally the prognosis in *D latum* infection is also good, and even the severe anæmia that develops in some subjects is easily curable at least in those who have no background of pernicious anæmia

DWARF TAPEWORMS

Geographical distribution —Both these tapeworms are cosmopolitan in their distribution but *Hymenolepis nana* shows a patchy distribution with here and there hyperendemic areas *e g* in India and Argentina for which there is no obvious explanation. *H diminuta*, of which the rat is the true definitive host has been reported in man mainly in India Russia Japan Italy and the southern United States

ÆTIOLOGY

Both dwarf tapeworms have the same general morphological characters as the large tapeworms

Life cycles and morphology *H nana*.—The eggs are subspherical 30 to 45 microns in diameter they have an outer vitelline membranous covering and an inner shell with small projections at the poles from each of which arise 4 to 8 filaments and they contain an onchosphere with three pairs of hooklets

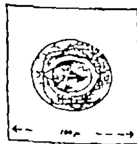


Figure 165 The egg of *Hymenolepis nana*

An egg is ingested by man and after passage through the stomach the onchosphere emerges and penetrates a villus in the small intestine where it develops into a cysticercus after about five or six days this larva migrates into the lumen attaches itself by its scolex to the mucous membrane and develops into an adult (25 to 40

mm in length with a maximum breadth of 1 mm.) From the time of ingestion of the egg the adult worm becomes mature in about two weeks and when it is mature the terminal proglottid disintegrates and releases about 180 eggs into the intestinal canal. Normally these are passed out with the stools and the cycle is completed but there is strong evidence that they may hatch in the intestinal canal (whether for this to occur it is necessary for them to be returned to the stomach by reverse peristalsis is not clear) and by a process of endo-auto-infection again go through the whole developmental cycle in the same individual. Reinfection by the external route also occurs

H diminuta — The egg is similar to that of *H nana* it is subspherical, 60 to 80 by 72 to 86 microns but has a slightly thicker outer covering and no filaments between the two membranes

The egg is ingested by an arthropod intermediate host (a large variety from grain moths earwigs cockroaches and millipedes to flea larvæ, have been incriminated) where it develops into an onchosphere and finally a cysticercus in due course the arthropod is ingested by man or other definitive hosts e g rodents in whose intestine it develops into the adult worm (20 to 60 cm in length with a maximum breadth of 4 mm.) The mature terminal proglottids disintegrate and release the eggs which are passed out with the stools



Figure 156 The egg of *Hymenolepis diminuta*.

Epidemiology —Man is probably the only important source of *H nana* infection it usually is a family household or institutional infection Children show the highest incidence In the United States eggs are found in about one per cent of all stool specimens in Calcutta a slightly higher infection rate was found and in Argentina a 9 per cent infection rate amongst a group of children has been reported.

H diminuta is relatively rare and is usually associated with low sanitary standards where murine parasites and other arthropods may be accidentally consumed with food. Infection has occurred through the consumption of insects infesting prepared cereal foods (Chandler 1922)

Pathology and symptomatology —*H nana* invades the mucous membrane during its larval stage secreting toxins and allergins and heavy infections cause a considerable degree of toxæmia which are clinically manifested by convulsions giddiness and even epileptiform attacks. Abdominal discomfort is a common complaint, and watery diarrhœa possibly of allergic origin is sometimes associated with this infection.

There is usually a moderate degree of eosinophilia up to 16 per cent.

H diminuta infection is not usually associated with any symptoms.

Diagnosis —This is made by the identification of the characteristic eggs in the fæcal smear or by the concentration technique (see p 590) or after anthelmintic treatment—possibly for other worm infections—by the finding of the whole or part of an adult worm in the stools

Prevention —Improvements in general sanitation and personal hygiene are indicated As auto-infection is common special attention must be paid to hand washing after defæcation and before meals Treatment will also be an important measure every infected person in a household or institution must be treated.

Treatment.—The treatment of *H nana* infection is complicated by the fact that both auto-infection and reinfection are common. It is therefore advisable to prescribe an anthelmintic that can be taken over a relatively long period or repeated often. Gentian violet meets this requirement

Diagnosis and treatment of intestinal helminths

Worm	Incubation period in weeks	Findings in faeces: Stage	Findings in faeces: Constancy	Eosinophilia	Drug or drugs of choice and adult dose
Ascaris lumbricoides or round worm	8	Egg	Numerous	++	Oil chenopodium—1 c cm + tetrachlorethylene—3 c.cm or hexylresorcinol—1 gramme
Trichuris trichiura or whipworm	12			+	Leche de Higuerón—2 ounces or hexylresorcinol—1 gramme or tetrachlorethylene—3 c cm
Enterobius vermicularis or threadworm.	8		Scanty	+	Gentian violet—1 × 3 grains for 8 days followed by second similar course after 7-day interval
Ancylostoma duodenale or hookworm	5		Numerous	++	Tetrachlorethylene in 4 c cm in saturated sodium sulphate—1 oz or hexylresorcinol—1 gramme
Strongyloides stercoralis	4	Larva	Irregular	++	Gentian violet (enseal) 1 × 3 grains for 17 days.
Trichostrongylus	(5)	Egg	Constant	++	As for hookworm
Taenia solium or pork tapeworm	6–12	Proglottid	Irregular	++	
Taenia saginata or beef tapeworm.	10–12			++	Felix mas—20 minims × 3 in gelatine-coated capsules orally or 00 minims in saturated sodium sulphate by duodenal tube or carbon tetrachloride—3 c cm
Diphyllobothrium latum or fish tapeworm	5–6	Egg	Periodic	++	
Hymenolepis nana or dwarf tapeworm	2			++	Gentian violet—1 × 3 grains for one week or hexylresorcinol—1 gramme

best it is given for one week only in the daily doses recommended strongyloidiasis (see p 607)

Hexylresorcinol is also a benign drug that can be repeated It w be advisable to give this in the doses advocated for ascariasis (see p 578 but it should be given twice with a one-week interval

In view of the fact that a multiple infection may arise in an individua from the infection by a single worm by means of auto-infection, even i reinfection can be excluded complete eradication of the infection must be achieved If no eggs are found at weekly examinations over a period of one month cure may be assumed.

For the treatment of *H diminuta* infection provided the source of infection has been eliminated, a single efficient treatment will be sufficient. Either of the above drugs could be used but the oleo-resin of *Aspidium filix-mas* is considered to be more specific

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TRICHINOSIS

Introduction—Trichinosis, or infection with the worm *Trichinella spiralis* (Owen 1835) Failliet, 1895 is in no sense a tropical disease The geographical distribution in fact indicates that a warm climate has some inhibitory effect on the infection as it is more common in the northern than the southern United States and is apparently absent from large areas in the tropics where it is hard to account for its absence on dietary considerations alone.

Historical.—Between 1828 and 1835 several British workers reported the finding of the larval stage of this worm in man. Similar reports followed from Germany, Holland, and North America. The infection was found in the pig in North America in 1846. Important observations on the life cycle were made by Leuckart and Virchow between 1855 and 1859, but it was Zenker who in 1860 pointed out the clinical importance of the infection and Virchow estimated that 90 per cent of the population of his country was infected. More attention was attracted to the infection in Germany than in other countries; it is therefore of interest that it is still so prevalent there.

The public-health importance of the disease has been fully recognized for at least 80 years, yet recent work, stimulated by a few severe outbreaks in the United States and in England, has shown that the infection is very prevalent in both of these sanitarily advanced countries. Wright and his colleagues (1943) have shown that 1 in every 6 persons in the United States is infected.

EPIDEMIOLOGY

Geographical distribution.—Published data probably give a poor idea of the real distribution, but it is certainly prevalent in Great Britain (Sheldon 1941), in many European countries, and in the United States (from Boston in the north 27.6 per cent, to New Orleans in the south 3.5 and 6 per cent). Cases have been reported from Kenya, Uganda and Tanganyika and from Brazil and Chile, but evidence that it occurs elsewhere in Africa, in Asia or in Australia is absent. In India Maplestone and Bhaduri (1942) reported finding *Trichinella spiralis* in a single cat, after failing to find it in 100 dogs, 100 pigs, 100 rats and 73 cats whose diaphragms were examined specifically for this infection by the digestion extraction technique, and after a study of the literature for the preceding 70 years they could find no records of the infection in man or animals in that country.

Distribution in population groups.—For all practical purposes the flesh of the pig is man's only source of infection, and the investigations of Wright and his colleagues (*loc. cit.*) showed the infection in only one of the two hundred Jews included in their investigation. The infection rate and clinical evidence indicate that the disease is more common in country than in town populations. There are two factors here—the better inspection of the pork in the cities to account for the lower infection rate, and the lack of concentration of infected material, as would be likely to occur in the country when a heavily infected pig would probably be distributed to a few families only, to account for the lower morbidity rate in cities.

Sex.—In several populations the infection rate has been found higher in women than in men. This has been accounted for by the practice of eating uncooked sausage meat in particular, that is apparently common amongst women in these populations.

ÆTIOLOGY

The causal parasite.—*Trichinella spiralis* is a small nematode worm; the female adult is about 3 millimetres long and 0.05 to 0.1 mm. in diameter and the male about half this size. The larvæ are about 100 microns long by 6 microns in diameter.

Hosts.—The cycle can be completed in one host species, but two individuals are necessary. The common hosts are pigs, dogs, cats and rats, and in certain countries bears, but any carnivorous animal may be infected. Rats which are cannibalistic are probably the most important reservoir of infection, and the pig is the important source of infection to man, although many fatal infections have been acquired from bear meat. Man is only an incidental host and under normal conditions constitutes a *cul-de-sac* for the parasite.

The life cycle —Encysted larvæ are ingested and the gastric juice digests the cyst wall sufficiently for the larvæ to escape in the duodenum. They penetrate the mucosa superficially and in from five to seven days develop into adults The worms mate probably in the crypts the male dies and is passed out with the fæces and the female again burrows deeply into the mucosa and produces 1,500 larvæ over a period of about six weeks The larvæ penetrate the lymphatics and venules, and eventually reach the systemic blood stream and come to rest in striped muscle They appear to prefer muscles such as those of the diaphragm inter costal spaces tongue larynx and abdomen, that are constantly active (the low glycogen content appears to be the factor as insulin increases and *glucose decreases the number of larvæ that will encyst*) but they will also encyst in certain skeletal muscles (*e g* the biceps) and rarely in other organs and tissues A boat shaped fibrous capsule is formed around the larva within which it grows to about one millimetre in length and lies curled up. The host is then eaten by another carnivore and the cycle is complete

Man may take the place of the host but in this case the cycle will not ordinarily be completed.

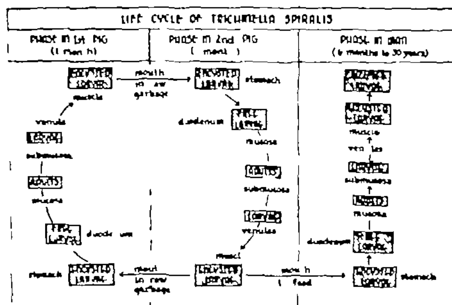


Figure 157

Immunity —There is evidence that rats acquire an immunity to subsequent infection after the first infection incident Actual proof that this is so in the case of man is wanting but the hypothesis would explain why the morbidity rate is so low in the presence of a high infection rate only those who received a heavy dose of infection at the time of their *first* exposure would show any morbidity However larvæ of apparently different ages have sometimes been found in one individual.

PATHOLOGY

The pathological changes produced in man by this infection can be conveniently divided into three phases The first phase includes the period of invasion of the infecting larvæ their development into adults their mating and the subsequent re-entry of the female into the mucosa. This may cause a considerable reaction in the mucosa with cellular infiltration

œdema some necrosis of the superficial layers of the mucous membrane possibly a little hæmorrhage and considerable outpouring of fluid into the intestinal canal.

The second phase commences with the parturition of the female the migration of the larvæ through the tissues, their destruction in some tissues and their coming to rest and encystment in the muscles. When these come to rest in their chosen site, there is an immediate tissue reaction in which eosinophils and large mononuclear cells take a prominent part, later fibroblasts appear and a thin fibrous capsule is laid down around each of the larvæ.

This boat shaped capsule containing the curled up larva lies between the muscle fibres with its long axis parallel to them. Some changes are evident in the surrounding muscle swelling of the muscle fibres, proliferation of interstitial tissue or in some cases degeneration of the muscle fibres

In other tissues in which the larvæ are not able to encyst, for example in the myocardium and the central nervous system there is evidence that they will nevertheless migrate and cause a very considerable cellular and inflammatory reaction to their toxins which leads to the destruction of the larvæ and not infrequently in severe infections to the death of the host.

The third phase is a quiescent one cysts will remain viable for a very long time, 30 years has been suggested (Craig and Faust, 1943), but as time goes on the surrounding fibrous capsule becomes thickened, and does not appear to allow much further escape of metabolites. Eventually the capsule may become calcified and in heavy infections these calcified cysts may cause a certain amount of muscular dysfunction.

Blood picture.—The eosinophil count is constantly high except in debilitated subjects It may rise to 6 000 per c.mm. (over 60 per cent) in the acute stages but it will tend to decrease later however an eosinophil count of 1 000 per c mm. or more may be found in an infected subject for several years

SYMPTOMATOLOGY

The severity of the clinical picture will vary almost exactly with the weight of the infection and the vast majority of infections are light and symptomless throughout. On the other hand there are a few cases in which certain grave symptoms can undoubtedly be traced to cardiac and cerebral involvement in heavy infections these rarer clinical manifestations will not be described here

It is convenient to consider the clinical course as being divided into three stages that correspond roughly to the three phases of the pathological picture Firstly there is the gastro-intestinal stage which may commence within twenty four hours of the ingestion of the infected meat and last for several days, often overlapping the second stage. This first stage corresponds to the period of activity of the larvæ and adults in the mucosa of the duodenum and probably ends when the female penetrates more deeply and commences to bring forth larvæ

The second or the toxæmic stage characterised by œdema, swellings and pyrexia and later by hæmorrhages pain in the muscles and other localising symptoms commences on the seventh to the tenth day with the parturition of the female and lasts as long as she is discharging larvæ it covers the period of destruction of the larvæ in unsuitable tissues and their encystment in suitable ones a period of perhaps six weeks. The subdivision of this stage into two periods that is frequently made in the

nature seems to the writer artificial as the phase in the life of the parasite is a continuous one

The last is really the convalescent stage in which the patient is recovering from the effects of the toxæmia but may have some residual disabilities as a result of the presence of encysted and possibly calcified larvæ

The gastro intestinal stage—It is apparently only in very severe infections that this stage is prominent In such cases there is severe watery diarrhœa often with vomiting so that the condition may simulate cholera and sometimes there is a little blood and mucus suggesting dysentery In moderately severe infection in which the patient comes under medical observation only when the symptoms of the second stage appear it will sometimes be possible to obtain a history of diarrhœa and indigestion a few days earlier but in the majority constipation will be reported

The toxæmic stage—The most constant and prominent symptom is swelling of the eyelids The patient may wake up in the morning with the eyes completely closed, and even with œdematous conjunctivæ everted and bulging The rest of the face may also be swollen and there may be swellings in other parts of the body The conjunctivæ are usually injected

The temperature is almost constantly raised usually up to 101 or 102° F and there is often a remittent type of temperature lasting for one two or three weeks or even longer

There is sometimes urticaria and other rashes have been described.

As well as severe frontal headache which is another very constant symptom, lethargy and apathy or anxiety and irritability have been observed in a considerable percentage of cases

Cough is common and hæmoptysis occurs rarely

About the third day after the swellings have appeared there will often be pain in the various muscle groups so that breathing becomes laboured and mastication and deglutition difficult and in fact all muscular movements particularly after a period of rest, are painful Pains may be slight or very severe and are often described by women as being as intense as labour pains They may last for one day or for several weeks

In this stage if the fever continues for a month or so there will be considerable emaciation and very great weakness with nervous and mental symptoms that suggest the typhoid state

A somewhat unusual symptom hæmorrhages under the nails and extreme tenderness of the tips of the fingers has been noted in about 10 per cent of clinical cases

In fatal cases death takes place during this second stage

The final stage—In this stage the patient recovers from the weakness and emaciation of the toxæmia and fever There are often residual pains and muscular pains that may persist for many months, and muscular weakness that may last for years. Calcified cysts can seldom be felt but can be seen by careful radiography

DIAGNOSIS

This will have to be considered under four headings (*a*) clinical and epidemiological, (*b*) parasitological (*c*) immunological and (*d*) post mortem examination.

(*a*) **Clinical and epidemiological**—A clinical diagnosis is unlikely to be made unless there is an epidemic or the patient gives a clear history of having eaten raw or insufficiently cooked meat that he suspects but in either of these cases the swelling of the face in the absence of any renal or cardiac cause the febrile attack in the absence of any demonstrable

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The severity of the clinical picture will vary almost exactly with the weight of the infection and the vast majority of infections are light and symptomless throughout. On the other hand there are a few cases in which certain grave symptoms can undoubtedly be traced to cardiac and cerebral involvement in heavy infections these rarer clinical manifestations will not be described here

It is convenient to consider the clinical course as being divided into three stages that correspond roughly to the three phases of the pathological picture Firstly there is the gastro-intestinal stage which may commence within twenty four hours of the ingestion of the infected meat and last for several days often overlapping the second stage This first stage corresponds to the period of activity of the larvæ and adults in the mucosa of the duodenum and probably ends when the female penetrates more deeply and commences to bring forth larvæ

The second or the toxæmic stage characterized by œdema swellings and pyrexia and later by hæmorrhages pain in the muscles and other localizing symptoms commences on the seventh to the tenth day with the parturition of the female and lasts as long as she is discharging larvæ it covers the period of destruction of the larvæ in unsuitable tissues and their encystment in suitable ones a period of perhaps six weeks. The subdivision of this stage into two periods that is frequently made in the

nature seems to the writer artificial as the phase in the life of the parasite is a continuous one

The last is really the convalescent stage in which the patient is recovering from the effects of the toxæmia but may have some residual disabilities as a result of the presence of encysted and possibly calcified larvæ

The gastro intestinal stage—It is apparently only in very severe infections that this stage is prominent In such cases there is severe watery diarrhœa often with vomiting so that the condition may simulate cholera and sometimes there is a little blood and mucus suggesting dysentery In moderately severe infections in which the patient comes under medical observation only when the symptoms of the second stage appear it will sometimes be possible to obtain a history of diarrhœa and indigestion a few days earlier but in the majority constipation will be reported

The toxæmic stage—The most constant and prominent symptom is swelling of the eyelids The patient may wake up in the morning with the eyes completely closed and even with œdematous conjunctivæ everted and bulging. The rest of the face may also be swollen and there may be swellings in other parts of the body The conjunctivæ are usually injected.

The temperature is almost constantly raised usually up to 101 or 102 F., and there is often a remittent type of temperature lasting for one two or three weeks or even longer

There is sometimes urticaria and other rashes have been described

As well as severe frontal headache which is another very constant symptom, lethargy and apathy or anxiety and irritability have been observed in a considerable percentage of cases

Cough is common and hæmoptysis occurs rarely

About the third day after the swellings have appeared there will often be pain in the various muscle groups so that breathing becomes laboured and mastication and deglutition difficult and in fact all muscular movements particularly after a period of rest are painful Pains may be slight or very severe and are often described by women as being as intense as labour pains They may last for one day or for several weeks.

In this stage if the fever continues for a month or so there will be considerable emaciation and very great weakness with nervous and mental symptoms that suggest the typhoid state

A somewhat unusual symptom hæmorrhages under the nails and extreme tenderness of the tips of the fingers has been noted in about 10 per cent of clinical cases

In fatal cases death takes place during this second stage

The final stage—In this stage the patient recovers from the weakness and emaciation of the toxæmia and fever There are often residual pains and muscular pains that may persist for many months, and muscular weakness that may last for years. Calcified cysts can seldom be felt but can be seen by careful radiography

DIAGNOSIS

This will have to be considered under four headings (*a*) clinical and epidemiological ,(*b*) parasitological (*c*) immunological and (*d*) post mortem examination.

(*a*) **Clinical and epidemiological**—A clinical diagnosis is unlikely to be made unless there is an epidemic or the patient gives a clear history of having eaten raw or insufficiently cooked meat that he suspects but in either of these cases the swelling of the face in the absence of any renal or cardiac cause the febrile attack in the absence of any demonstrable

infection, and the severe cramps in the muscles in the absence of dehydration and hypochloræmia will be highly suggestive. A high eosinophil count without any other apparent cause will add support to this diagnosis.

(b) Parasitological.—Only by a very unlikely chance will the adults or the larvæ be found in the stools, or the latter in the blood or other fluids but the search for encysted larvæ in muscle biopsy specimens is a useful method of diagnosis as many as 800 larvæ per gramme have been recovered from non fatal cases The piece of muscle can be examined, pressed between the slides or after digestion in artificial gastric juice for 24 hours at 37 C (*vide infra*)

(c) Immunological.—The intradermal test has been used widely for demonstrating sub-clinical infection The most recent technique gives results that are highly specific for this infection although, with lower dilutions of the antigen false positives are given in the presence of trichocephalus infections A blood precipitin test is also employed it is more difficult to interpret and should be used only as confirmatory evidence

Technique.—The antigen* is prepared from desiccated larvæ extracted from infected pork.

For the intradermal test the dilution should be 1 in 10,000, of which 0.2 c.cm is injected into the skin of the forearm In a positive case a weal of at least 7 mm in diameter with pseudopodia will appear and this will be surrounded by a ring of erythema of at least twice this breadth

A control in which the solvent is used without any antigen must be done at the same time

The delayed reaction which may occur after a delay of 24 hours is less specific.

The precipitin test is done with a 1 in 100 dilution of the same antigen. In a micro-tube a small quantity of the antigen solution is floated on top of an equal amount of the patient's serum, and the reading is made after one hour in the 37°C incubator

These tests become positive between the second and third weeks and remain positive for several years

(d) Post mortem examination.—The diaphragm is usually the best source of trichinella larvæ A piece of this is cut into a thin slice which is pressed between two strong slides and then examined under the low power lens of the microscope for encysted larvæ

A more satisfactory method is by digesting the muscles, as follows —

Technique.—Digest about 50 grammes of muscle in 0.7 per cent hydrochloric acid—1.0 per cent of pepsin, 20 c.cm to a gramme of muscle, overnight. The mixture should if possible be stirred periodically The digested material is placed in a large glass funnel to which a short length of rubber tube with a stop-cock is attached. The encysted larvæ fall to the bottom of the funnel and can be drawn off by opening the stop-cock. A count can also be made by this method.

PREVENTION

Personal prophylaxis can be achieved by refraining from eating lightly cooked or undercooked pork. Refrigeration to -15 C for 24 hours will destroy larvæ but ordinary refrigeration and salting or smoking will not

The only effective public health measure generally practised is the inspection of pork. Light infections are very liable to be overlooked but the fact that the infection is much rarer in towns where generally inspection is adequate than in the country districts where it is not is evidence of the value of this procedure.

Education and propaganda amongst small pig raisers in country districts to discourage raw garbage feeding and to encourage the proper

* Prepared antigen can be obtained from Eli Lilly and Co and probably other drug manufacturers

disposal of pig viscera and of the carcases of pigs dying of disease is important. Rats also being common hosts should be destroyed or at least kept away from the animal food store.

TREATMENT

No specific for this infection is known and from the nature of the infection and the difficulty of early diagnosis it seems doubtful whether a specific would be of very great value were one discovered unless it were capable of killing the encysted larvæ in the muscles. Treatment must therefore be symptomatic and palliative.

The administration of calcium in the form of calcium gluconate for example has been suggested in order to hasten the encapsulation of the larvæ.

PROGNOSIS

It must be obvious that the prognosis in the vast majority of cases is excellent as they do not show any symptoms at all. On the other hand in the very heavy infections in which gastro-intestinal symptoms appear the prognosis should be guarded as many deaths have been reported. In such cases the absence of a high eosinophilia is a bad prognostic sign.

It has been estimated that 5,000 larvæ per kilogramme of body weight will usually prove fatal. However 800 larvæ per gramme of muscle have been recovered by biopsy in a non fatal case. The two statements are not necessarily contradictory.

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FILARIASIS*

This section has been written with the aid of notes by Dr S. S. Rao, especially on the morphology of the parasites, on the history and distribution of filariasis, and on *Wuchereria malayi* infection.

FILARIASIS DUE TO *WUCHERERIA MALAYI*

FILARIASIS DUE TO *LOA LOA*

ONCHOCERCIASIS

Introduction.—Filariasis is the term applied to the infections and to the diseases caused by the infections, in man and animals by certain nematodes of the super family Filarioidea that were at one time generally placed in the now superseded genus Filaria namely —

Wuchereria bancrofti (Cobbold 1877) Seurat, 1921
Wuchereria malayi (Brug 1927) Rao and Maplestone, 1940
Loa loa (Cobbold 1864) Castellani and Chalmers 1913
Mansonella ozzardi (Manson 1897) Faust 1929

For the other two important infections by nematodes of the super family Filarioidea namely —

Onchocerca volvulus (Leuckart 1893) Railliet and Henry 1910
Acanthocheilonema perstans (Manson 1891) Railliet, Henry and Langeron, 1912

The words onchocerciasis and acanthocheilonemiasis are commonly used although both worms are often referred to as filarial worms.

The morbid changes that occur in filarial infections are brought about by the mature larvæ and the adult worms passing through or lodging in the tissues especially in the lymphatics and causing local reactions

Mansonella ozzardi is confined to the Americas where it has a limited distribution in northern Argentina in the countries along the north coast of South America in Mexico and in the West Indies The adult worms live in the body cavities and apparently produce no symptoms. The microfilariæ are very small unsheathed and very similar to those of

Acanthocheilonema perstans. The infection has been transmitted experimentally by the gnat *Culicoides furens*.

Acanthocheilonema perstans has a wide distribution in tropical and northern Africa and in the coastal area of tropical and sub-tropical South America. The clinical condition that it produces is ill-defined and many workers believe it to be a non-pathogenic parasite. The microfilariæ are unsheathed, much finer (less than 5μ) and shorter (less than 200μ) than those of the pathogenic filariæ and should never give rise to confusion. The intermediate hosts are species of *Culicoides*.

No further reference will be made to either of these two infections.

FILARIASIS DUE TO *WUCHERERIA BANCROFTI*

Historical.—Although filariasis in its grosser manifestations was mentioned by ancient Indian writers, the term elephantiasis was apparently first used by Celsus to indicate leprosy and later by Galen to indicate both leprosy and true elephantiasis. A third disease, Madura foot, was also generally confused with leprosy and elephantiasis until about the eighteenth century. In 1750 Hillary gave a full and lucid account of the elephantoid leg wherein he clearly differentiated this disease from leprosy. The classical researches of Danielssen and Boeck in 1848 on leprosy and those of Vandyke Carter in 1860 on mycetoma established clearly the true nature of these two diseases and their distinction from one another and from filariasis.

EPIDEMIOLOGY

Geographical distribution.—Of the human filarial parasites *Wuchereria bancrofti* has the most extensive distribution in the tropics and subtropics and occurs in regions from about 42° N. to about 38° S. in the eastern hemisphere and from about 30° N. to 30° S. in the western hemisphere.

In America the infection is common in Central America, in the West Indies, in British, Dutch and French Guiana, Venezuela, Brazil, Peru and Columbia. In the United States a considerable focus of infection, probably originally introduced from Africa, was discovered in South Carolina some years ago, but no fresh cases have been reported in recent years; it probably does not occur elsewhere.

It is common on the west coast of Africa, in Madagascar and the neighbouring islands of Mauritius and Reunion, in East Africa, and in Egypt and in North Africa.

In Europe, it is reported to occur in Spain (Barcelona), Hungary and Turkey.

In Australasia it is common in New Guinea, Papua and other islands and it occurs along the northern and eastern coasts of Australia. It is extremely common throughout the Pacific islands, such as Samoa and the Friendly Islands, Fiji, and the Gilbert and Ellice groups of islands.

In Asia it is especially prevalent in Arabia, India, Ceylon, Burma, the Malayan peninsula, the Philippines and the islands of East Indies, southern China and southern Japan. In some of these areas over 80 per cent of the population are infected.

In India the infection is extremely prevalent, but it is more or less confined to the coastal regions and to areas along the banks of the important rivers. West Bengal, Orissa, Travancore, Cochin and Malabar are the most heavily infected areas (microfilaria rate over 20 per cent to over 30 per cent). All these are low flat countries that have a high rainfall; they are water-logged for many months each year and the temperature and humidity are both high for over half the year; conditions are therefore very favourable for the breeding of mosquitoes and for the transmission of the infection. The moderately infected region (microfilaria rate between 5 and 20 per cent) include the rest of the east coast of India, East Bengal

Females measure from 50 to 100 mm. in length and from 0.2 to 0.3 mm in breadth The tail tapers gradually the tip is rounded The anus opens about 0.2 mm. from the tip of the tail The vulva opens on the ventral surface about 0 6 mm to 1.3 mm. from the anterior end. The vagina is a muscular tube forming a loop with a pyriform enlargement, and ends in the uterus the distal end of which is generally found filled with fully extended embryos ready to be discharged. At its proximal end, the uterus is divided into two branches which occupy the greater portion of the body and each terminates towards the tail end in an ovary Each branch of the uterus contains eggs and embryos in various stages of development.

The ova and embryos —These are found in the posterior end of the uterus Their dimensions vary according to the stage of their development when fully developed they measure about 40 microns in length and 25 microns in breadth. The ovum does not possess a true shell but only a membrane which becomes stretched to form the so-called sheath of the microfilaria

The measurements of the individual microfilariæ (embryos) of *Wuchereria bancrofti* in ordinary thick smears when plotted on graph paper exhibit a smooth curve and there is no marked difference in their measurements in the wet and the dry states the average length of the embryo itself is 290 microns, the breadth 6 to 7 microns while the length of the sheath is 359 microns (Iyengar 1939)

The embryo shows well marked cuticular striations The cephalic space is generally smaller than the breadth of the embryo in this region. The tail tapers gradually to a rounded tip and is free from nuclei

Life cycle of the parasite.—The adult filarial parasites live in the lymphatics of man mainly in those of the pelvic region. They are known to live there for a considerable period of time without producing obstruction to the lymphatic circulation The gravid female discharges embryos periodically these embryos reach the blood stream and circulate there The embryos exhibit a nocturnal periodicity* in the blood stream except in

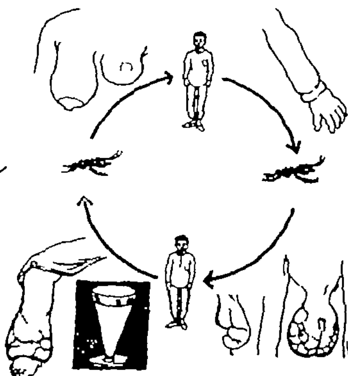


Figure 158 Showing the cycle of infection from man through mosquito to man As the human carrier develops lymphatic obstruction and filarial dis- ceases to be ner of the infectio

* *Microfilarial periodicity*—The maximum ... rofilariæ is fou the hours of 10 p.m. and 2 a.m and never ... This perio device on the part of the filarial worm (or of ... propagation as it is only observed in countries where the ... ctor i a n

Fiji and certain other Pacific islands where they show no special periodicity. They do not develop further in the blood but are taken up by the intermediary host, the mosquito, where the next stage of development occurs.

Ordinarily a drop (20 c.mm.) of peripheral blood of an infected individual may contain anything up to 600 embryos. It has been found that while a moderately high concentration (about 15 embryos per drop of blood) is necessary for the successful transmission of the infection, a much higher concentration of microfilariæ, i.e. 100 or more embryos per drop, is fatal to the mosquito.

The development of the filarial embryo in the intermediary host, the mosquito, may be briefly described as follows:—

As the mosquito feeds on the blood of an infected individual, the embryos (microfilariæ) are taken in by the mosquito and enter its stomach. With the progress of digestion in the stomach, the blood plasma becomes thickened. At this stage the embryos escape from their sheaths and enter the thoracic region of their mosquito host. It has been shown by Iyengar (1939) that within ten minutes most of the embryos enter the thorax and lie in between the thoracic muscle fibres, where at first they are comparatively inactive. After two days, the first larval stage embryos measure about 124 to 250 microns by 10 to 17 microns. Many changes take place in the structure of the embryos and the tail becomes reduced to a stump (sausage stage). After the third day, the development of the body cavity, œsophagus and the anus takes place, and at the end of seven days the larvæ (second stage) measure 225 to 300 microns by 15 to 30 microns. Caudal papillæ are now observed.

During the second week moulting occurs and under optimum conditions the metamorphosis is complete by the tenth or eleventh day. The infective third stage (filariform) larvæ, which now measure 1,500 to 2,000 microns by 18 to 23 microns, show an alimentary canal and a tri-lobed tail. They leave the thorax, migrate to the proboscis and eventually reach the interior of the labium. They are generally seen to move in pairs. When the mosquito feeds, the larvæ escape at the junction of the labium with the labella and enter through the puncture made by the mosquito or even through the unbroken skin.

The larvæ find their way into the peripheral lymphatics. Their subsequent progress and eventual fate will depend to a great extent on the host's reactions, but under conditions of perfect symbiosis the cycle will be completed as follows. The larvæ migrate centripetally and eventually reach the large lymphatic trunks where, having developed into male and female adults, they mate. The female discharges the microfilariæ which are carried *via* the lymphatic trunks into the subclavian veins and the systemic circulation.

This is the outline of the cycle as it occurs when symbiosis is perfect, and it accounts for none of the pathogenesis associated with the infection; when the host's tissues react to the presence of the worm, these reactions

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In Fiji, *Aëdes variegatus*, which is a diurnal feeder, is the important vector and the microfilariæ are found in the blood throughout the 24 hours in this and other Pacific islands. Many theories have been put forward to explain the mechanism of this periodicity—that it is due to light, directly repelling the embryos or adversely affecting their activity, to the inactivity of the host at night, to chemotaxis from the bite of the mosquito, to defective oxygen supply, or to mid-day parturition of the worm and the daily death of the microfilariæ (Lane 1933)—but no theory is entirely satisfactory. The ingenious, though unlikely, theory regarding mid-day parturition—which itself requires further explanation—has been disproved by several workers who have shown that even in another host the life of the microfilaria is over a week.

If the host changes his habits and sleeps during the day, the microfilariæ that he harbours will change their periodicity correspondingly in about three days.

and their effect on the cycle will be described below under the heading of Pathology

It is however possible that in some instances after the adult worms have mated, they, *or at least the females* migrate centrifugally to the lymphatics of the extremities and genitals for parturition. This hypothesis—for which there is analogy but no experimental proof—would help to explain certain observed phenomena, though it is believed that these can be explained almost as well on other grounds (*vide infra*)

From the entry of the mature larvæ to the appearance of microfilariæ in the blood of the host is usually stated to be about one year but there *is evidence that the interval may be much longer*

Correlation between filarial infection and filarial disease.—It is no longer necessary to discuss this from the point of view of establishing the causal relationship between filarial infection and the various clinical manifestations of the disease for the subject is only one of historical interest, as far as the commoner clinical manifestations of filariasis are concerned

Many of the early workers, *e g* Low (1908) and O'Connor (1923), *noted the correlation between the incidence of filarial disease and the* blood microfilaria rate *in the community*, and recently Iyengar (1938) found a positive correlation coefficient of 0 7644 between the microfilarial *rate and filarial disease* in 216 localities in Travancore (India) In chyluria due to filarial infection, microfilariæ are usually found in the peripheral blood Ray *and Rao (1939) found* them in 78 per cent of their cases

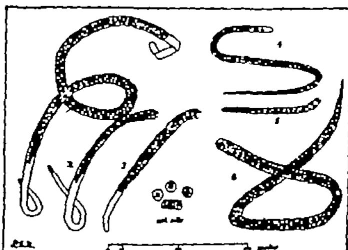


Figure 159 Microfilariæ of the important filarial worms.

Sheathed	Unsheathed
(1) *Wuchereria bancrofti.*	(4) *Mansonella ozzardi.*
(2) *Wuchereria malayi*	(5) *Acanthocheilonema perstans.*
(3) *Loa loa*	(6) *Onchocerca volvulus.*

On the other hand most (though not all) observers have found a very definite negative correlation between blood microfilarial findings and elephantiasis *in the individual*. In India Acton and Rao (1930) found microfilariæ in only 5 7 per cent of cases of frank filarial elephantiasis whereas they found them in 14 7 per cent of the symptom free population of the same area. In a population in which there was a 92.8 per cent filarial disease rate, Rao (1941) found a microfilaria rate of 8 4 per cent in those with elephantiasis against 54.3 per cent in those without it. And Iyengar (1938) in an investigation in several localities in India, involving over four thousand persons of whom over five hundred had clinical filariasis, found that the microfilaria rate was on an average about three times as great amongst those showing no clinical evidence of the infection as amongst those with elephantiasis

The usual explanation for the higher microfilaria rate in subjects without clinical lesions, namely that the lymphatic channels are mechanically blocked by the worms and the reaction that they cause so that no microfilariæ can get into the circulation (*vide infra*) seems scarcely

adequate to account for this very striking difference It seems that one must visualize a general reaction of an allergic or an antibody nature on the part of the host otherwise one would expect the worms in those areas where the blocking was as yet incomplete to provide some microfilariæ On the other hand the absence of microfilariæ noted in the earliest stages of infection is almost certainly due to the immaturity of the worms and/or to their failure to mate

Conditions favourable to the development of the larvæ in the mosquito —The stages of the development of the larvæ of *Wuchereria bancrofti* in mosquitoes outlined above require a mean atmospheric temperature of about 80 F and a humidity above 60 per cent Laboratory controlled experiments by Rao have shown that the development of the larvæ in the mosquito depends directly upon temperature and humidity the optimum conditions for the development have been found to be a combination of 80 F with 90 per cent humidity Under these condition the parasite is found to complete its full development in the mosquito within seven days Observations carried out in India (Calcutta and Cuttack) and in China have shown that the times for development in the mosquito under natural conditions vary according to the temperature and humidity from two weeks in the summer to three weeks or more in the winter months Delay in the development of the filarial embryo in the mosquito reduces the chances of the infection being transmitted because in many instances the embryo will fail to reach the third larval the infective stage

Intermediate hosts —*Culex fatigans* is the common host in Egypt India South China, Formosa Celebes the East Indies the Philippines Australia the West Indies and Brazil. In mosquitoes of other species and genera the complete developmental cycle will take place and one must assume therefore that they are potential vectors In some instances *e g* *Aëdes variegatus* var *pseudoscutillaris* in Fiji these are known to be the principal vectors Craig and Faust (1943) give the following as potential vectors —

Culex pipiens and *C pipiens* var *pallens* (Central China Japan and Egypt) *C habilitator* (St Croix, West Indies) *C fuscocephalus*, *C whitmorei* *C annulirostris* *C alis* and *C vishnui* (all from Dutch East Indies and Celebes) *Aedes ægypti* (West Africa, New South Wales St Croix and West Indies) *Aëdes variegatus* (Pacific islands) *Aëdes togoi* (Japan) *A tæniorhynchus* (St. Croix West Indies) *Tæniorhynchus pseudotitillans* (Malaya) *M uniformis* (Central Africa) *M juxtamansonia* (Brazil) *Anopheles albimanus* (Caribbean area) *A albitarsis* (Brazil) *A gambiæ* *A funestus* *A rhodesiensis* *A squamosus* (Sierra Leone) *A algeriensis* (Tunis) *A hyrcanus* var *nigerrimus* (Travancore) *A hyrcanus* var *sinensis* (Shanghai) *A barbirostris* *A subpictus* (both fresh and brackish water types) *A pseudojamesi* (*ramsayi*), *A varuna* *A philippinensis* *A pallidus* *A annularis* (*fuliginosus*) *A stephensi* *A sundaicus* (all in India) *A amictus* (North Queensland) *A barbirostris* var *bancrofti* (Dutch East Indies and Celebes) *A aconitus* (Dutch East Indies and Celebes) *A punctulatus* (New Guinea and Celebes) and probably *A maculatus* (Celebes)

It seems possible that the microfilariæ that are retained in the tissues behind the obstruction in the lymphatic vessels, or in the subcutaneous tissues are actively destroyed and provide the necessary sensitising (*sensu lato*) stimulus, whereas in lymph varix chyluria etc the microfilariæ reach the blood stream where they circulate until they are obsolete and are subjected to a gradual process of absorption with other circulating debris The observation of Iyengar (1933) that the longer the duration of the obstruction the lower the microfilaria rate would support this view

FACTORS AFFECTING ENDEMICITY

The four essentials for transmission are,

(i) the source of the microfilaria, which is always man,
(ii) the mosquito vector
(iii) susceptible man, and
(iv) links between (i) and (ii) and (ii) and (iii)

There is no reason to believe that race, age, or sex per se make any difference in the susceptibility of man to infection, or in the number of microfilariae that will circulate in his blood given therefore the source of infection and mosquitoes of a good transmitting species (of which there are many) the factors influencing the amount of filarial infection in any locality will be

(a) the density of the human population
(b) the density of the vector mosquito population, and
(c) the duration of the period of effective transmission each year*

But given a fixed human and a seasonally varying mosquito (e.g Culex fatigans) population, filarial incidence will depend not so much on (c) but more on the length of duration of the coincidence of the favourable periods in factors (b) and (c) that is on

(d) the duration of the coincidence between the peaks (or high plateaux) of the mosquito incidence and favourable temperature and humidity curves.

The density of the vector mosquito population (b) will depend on a *number of factors which will vary according to the species concerned* but the seasonal variations in the density will also depend to a great extent on temperature and humidity and the same ranges as in the case of factor (c), namely 80 F to 90 F and over 90 per cent will certainly be favourable for mosquito breeding but other contemporaneous factors may not be and therefore the peaks do not always coincide.

For example in Calcutta the most suitable period for transmission is from May to October but the peak of the Culex curve is later in the year so that Calcutta is an area of moderate endemicity whereas in many coastal towns in South India the transmission period lasts almost throughout the year, and such places are hyperendemic

We therefore have the equation

degree of endemicity = a × b × d

It will thus be seen why the disease is endemic in hot damp tropical climates and in coastal areas where an even temperature is the rule, why it is seen at its best in densely populated areas, especially in towns in which the Culex population is not controlled and why there is considerable variation in the intensity of the endemicity from place to place within these areas The more practical importance of this appreciation of the factors concerned in transmission will be its application to prevention (*vide infra*)

PATHOLOGY

As in other filarial diseases the pathological changes are caused by the adult and pre-adult worms passing through or lodging in the tissues and giving rise to local reactions in these tissues the circulating microfilariae themselves apparently produce no recognizable tissue reaction.

Morbid anatomy —There is evidence of tissue irritation from the point of entry of the mature larvae onwards The skin around where the

* Temperature and humidity are the main factors in determining the complete development of the filarial embryo in the mosquito so that transmission may take place a relative humidity of 90 per cent and a temperature between 80 and 90 F appear to be the most favourable (*vide supra*)

PLATE XXII



Fig. 1



Fig. 2



Fig. 3

PLATE XXIII

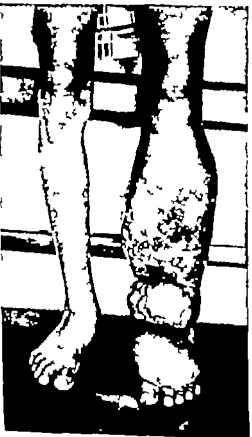


Fig. 4.



Fig. 5



Fig. 6.

larvæ penetrate may become thickened hard and red and this condition usually persists for some days The lymphatic channels through which the larvæ migrate show signs of irritation, apparently as a result of the action of some substance secreted by the larvæ The tissues respond by hypertrophy of the endothelial cells of the vessel walls

When the immature worm reaches a lymph node it must work its way through the lymph spaces between the trabeculæ and the lymphoid nodules of the cortex to reach the medulla During this passage considerable local reaction is caused when numerous mature larvæ constantly pass through a node the whole node increases in size and in a short time it is converted into a mass of eosinophilic granulation tissue and no longer contains any lymphoid tissue. As the lymph channels are obstructed by this granulation tissue lymph can no longer percolate through the node nor can the larvæ pass through it they are held up distally to the obstruction and there complete their development In some instances adult worms fail to mate and the sterile female after living in the lymphatics for some time and causing periodic reactions eventually dies and is absorbed or calcified In other cases the adult worms mate and the female undergoes parturition in this sub-optimal environment With the discharge of the embryos the uterine fluid—which is expelled at the same time—acting as a toxin causes **lymphangitis and/or lymphadenitis** (In sections of tissue containing worms a large number of desquamated endothelial cells derived from the endothelial lining of the vessel walls can sometimes be seen at the site of the vulval orifice of the worm, which is close to the head end.) In this way an obstruction is gradually formed to the centripetal flow of the lymph and the pressure rises in the obstructed lymph channels

The gravid female gives birth to living embryos intermittently probably for a few days in each month and this is the most likely explanation for the periodicity of the febrile attacks and other allergic signs and symptoms both local and general. When the gravid female ceases to produce embryos toxins are no longer excreted to the same extent and for the time being the inflammation subsides

The primary factor in the mechanical production of lymph varices is this intermittent rise and fall of the lymph pressure Clinically such varices are seen most frequently in lymphatics that are supported by loose tissue such as those around the superficial lymph nodes on the inner aspect of the arm etc or when the deeper lymphatics are involved the abdominal plexuses and those of the spermatic cord (*vide infra*)

The local reaction to the presence of a foreign body in a lymphatic vessel or in a lymph node may be such that the mature worm or even the immature worm is strangled or such worms may die of old age or for some other reason When this occurs there is an infiltration of lymphocytes plasma cells and eosinophils and the formation of giant cells which destroy the worm. Meanwhile new blood vessels are formed in the granulation tissue fibroblasts appear and eventually the remains of the worm are encapsulated and may become calcified. This process may be associated clinically with a sharp local inflammatory reaction and in some cases with a febrile attack. Later there will always be scar formation which will further interfere with lymph flow in this region

When the lymph flow is thus obstructed in the distal parts of the lymph system, the lymph pressure increases at first the deeper lymphatic vessels dilate then those of the subcutaneous tissues and finally the skin lymphatics Lymph ceases to drain from the tissues and the part becomes progressively more swollen Figures 1 and 2 (plate XXII) show this dilatation of the surface lymphatics and the separation of white fibrils and

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As long as the lymphatic obstruction is only partial or intermittent microfilariæ will find their way into the blood stream but if it is complete the larvæ are confined behind the obstruction in the œdematous and hypertrophic limb and do not appear in the blood stream Hence it is the rule that, in cases of chyluria and lymphatic varix of the cord microfilariæ are almost always found in the blood, whereas in elephantiasis of the limbs and genitalia they are frequently not found (*vide supra*)

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There is no reason to believe that tolerance is a fixed quality ,and it seems possible that many persons who are at first tolerant in course of time become intolerant. Further there will be degrees of tolerance just as there will be many grades of subjection to infection and it is not suggested that these four categories are sharply defined

If now, one of the possible common septic complications is added—such as an infection from the skin surface in elephantiasis or from some hollow viscus into which a lymph or chyle varix has ruptured or possibly a hæmatogenous infection from some septic focus *e g* an apical abscess or bowel focus—or if the rarer complication of hæmorrhage occurs it will be seen that a very large variety of clinical manifestations can be accounted for

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muscle by the lymph in the tissues Such tissue is known as *blubbery tissue* and when one cuts into it the lymph exude and the tissue collapses

In course of time the fibroblasts in the blubbery skin multiply and form new fibrous tissue which makes the skin dense and hard—the typical elephantoid skin The fibrous induration extends deep down into the lower layers of the skin as far as the sweat glands interfering with the lymphatics in that region and producing œdema followed by fibrosis around the sweat glands which are eventually destroyed, so that the skin in elephantiasis is always harsh and dry In the meantime the surface hypertrophy of the epidermis becomes more and more marked and fissures occur in the ill developed horny layer and allow micro-organisms to invade the corium. In these very large warty elephantoid limbs repeated attacks of inflammation originating at the surface and due to secondary bacterial infection are extremely common and increase the local hypertrophy

When the obstruction is in the deeper lymphatics the lymph is dammed back, causing **lymph varices** of the abdominal plexuses and spermatic cord these may rupture into the peritoneum kidney bladder or tunica vaginalis causing **lymph ascites lymphuria** and **lymphocele** or if the obstruction is proximal to the receptaculum chyli this will lead to a reflux of chyle into these plexuses and if they rupture **chylous ascites**, **chyluria** or **chylocele** will result.

The entrance of more and more mature filariæ into these dilated tortuous lymphatics keeps up the irritation of the vessel wall so that the endothelial cells hypertrophy and form a vascular granulomatous mass which projects into the lumen like a papillomatous growth The slightest trauma is likely to rupture the blood vessels in these papillomatous growths and cause bleeding into the lymph vessel with the production of **hæmaturia hæmatocele** etc

When the back pressure extends to the lacteals these may dilate and eventually rupture into the intestinal tract this reflux flow of chyle may cause **chylous diarrhœa** but a much more serious sequel will be infection of the dilated and damaged lacteals, from which infection may spread backwards to the larger lymph vessels so that when they rupture serious septic complications are likely to follow

As long as the lymphatic obstruction is only partial or intermittent microfilariæ will find their way into the blood stream but if it is complete the larvæ are confined behind the obstruction in the œdematous and hypertrophic limb and do not appear in the blood stream. Hence it is the rule that, in cases of chyluria and lymphatic varix of the cord microfilariæ are almost always found in the blood whereas in elephantiasis of the limbs and genitalia they are frequently not found (*vide supra*)

The importance of **secondary** bacterial infection is a controversial subject Some workers including Leiper (1924) Acton and Rao (1929) and Grace and Grace (1931), believe that staphylococcal or streptococcal infections play an important part in all the inflammatory processes of a filarial attack, whereas others question this and believe that most of the milder inflammatory reactions except those originating in the skin, can be attributed to the irritation of the filarial secretions and of the body of the worm itself and to an allergic response on the part of the host (O Connor 1932) All recent work has supported the latter view and has often shown the complete absence of septic organisms in the early inflammatory lesions The allergic lesions may be some distance from the actual worm and the supporting tissues around the genital organ e g the cord and testicle appear to be particularly prone to allergic reaction. However the more serious complications such as acute suppurating funiculitis peritonitis and septicæmia are obviously due to secondary infection, which

may have been hæmatogenous in origin but is more likely to have resulted from direct infection from some hollow viscus into which the varices have ruptured

The variations in the lesions produced —Various explanations have been suggested for the differences in the lesions produced by filarial infections in different individuals but the following explanation appears to the writer to have most support from his personal experience and from recorded data —

If the complication of sepsis is excluded, there are two factors concerned both of which are variable namely, (a) the tolerance of the subject to filarial metabolites and (b) the intensity of the infection to which he or she is subjected

The human host will fall into one of the four following categories —

(i) *Tolerant individuals subjected to few infected bites* their tissues do not react to the filarial metabolites so that the migration of the pre-adult worm and parturition of the adult cause little or no reaction, and no clinical symptoms but microfilariæ will always be found in the blood once the worms reach maturity

(ii) *Tolerant individuals subjected to a heavy infection* in course of time mechanical blockage of the lymph nodes may occur causing some static œdema lymph varix, or both without necessarily any lymphangitis or febrile reactions

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cases in which there is an increase in blood eosinophils suggests an ext medullary origin for the latter

A moderate eosinophilia is common in *cases in which there are mic* filariæ in the nocturnal blood but few or no *signs of lymphatic obstructi* During an acute attack of filarial lymphangitis, there is never any incre of eosinophils and they are not infrequently absent from the periphe blood.

Microfilariæ in the blood —Reference should be made to the abo paragraphs on microfilarial periodicity and on the correlation betwe filarial infection and filarial disease

We have found fewer microfilariæ in the sternal marrow than in t peripheral blood, both during the day and during the night.

Urine —There are no characteristic changes in the urine in ordinary case of filariasis

In chyluria the urine is typically a milky white but the colour not constant in a doubtful case the urine should be shaken up with eth or chloroform to see if it clears as it *will do if the milkiness is due* fat. If there is any doubt the urine should be examined again one four hours after a fatty meal. In chyluria as also in lymphuria t urine will coagulate on account of the presence of fibrinogen. If it set aside it will separate into three strata an upper milky stratum, middle pinkish one in which the clot will be seen and a lower stratu consisting of cells and debris

Microfilariæ will be found in about 50 per cent of the cases eith in the lowest layer or in the clot, or one can demonstrate them by droppi *a few threads of cotton wool into the urine allowing these to sink* the bottom and then recovering a thread and examining it under the lo power of the microscope

The fat content will vary from a trace to just over one per cent, an *the albumin from a trace to 0 6 per cent*

In lymphuria there is albumin and many lymphocytes but, exce for the possible presence of clots, the gross appearance of the urine is litt changed

In hæmatochyluria and hæmatolymphuria there will in addition b *red cells and some free hæmoglobin*

SYMPTOMATOLOGY

Classification —From the description of the pathological process given above it will be obvious that the clinical pictures produced ma be very varied. As has been indicated above there may be a short live skin lesion—redness and induration with some irritation—at the point o entry of the larvæ but this is inconstant and is seldom remembered b the patient it therefore need not be considered in the symptomatolog Otherwise the following *classification covers the commonest of the filari* syndromes —

A Signs and symptoms may be absent
B Lymphangitis and lymphadenitis.
  (i) Uncomplicated
  (ii) *Septic, which may subside or lead to*
  (iii) Abscess formation.
C Elephantiasis.
  (i) Uncomplicated
  (ii) Complicated by sepsis.
  (iii) Either may involve
    (a) The limbs.
    (b) The scrotum, penis or labia
    (c) The mamma

D Lymph varix, superficial or deep
  (i) Uncomplicated
  (ii) Rupturing and producing a variety of non-septic complications
    (a) Lymphorrhœa, of the groin or scrotum
    (b) Filarial synovitis
    (c) Lymphocele (hydrocele)
    (d) Lymphuria
    (e) Lymph ascites
  (iii) Bleeding, as a result of trauma and producing
    (a) Hæmatospermia
    (b) Hæmatocele
    (c) Hæmaturia or hæmatolymphuria
  (iv) Suppurating, before or after rupture

E Chyle varix
  (i) Uncomplicated
  (ii) Rupturing and producing a variety of non-septic complications
    (a) Chylocele
    (b) Chyluria
    (c) Chylous ascites
    (d) Chylous diarrhœa
  (iii) Bleeding may occur as in lymph varix and produce a parallel series of complications
  (iv) Suppurating before or after rupture

F General symptoms
  (i) Fever
  (ii) Allergic manifestations
    (a) Skin manifestations e.g. urticaria
    (b) Extra focal inflammatory swellings, especially of the genitals
    (c) Asthma

G Psychoneurotic manifestation

A full clinical description of each of the very numerous filarial manifestations classified above would be out of place here but notes are given below on the commoner ones and on those that seem to require some explanation As far as they are applicable the paragraph identification used above are followed

Incubation period—It is usually stated that microfilariæ first appear in the blood about one year after the larvæ have been introduced by the infecting mosquito but the time may probably be shorter and is often longer However this cannot be considered the incubation period of the *disease* which is even more variable Some indication of this can be obtained from the age at which persons born in an endemic area first show symptoms In many filarious countries it is seldom that evidence of lymphatic obstruction appears within 15 years of the date of arrival in an endemic area although in such cases there will often be a history of periodic febrile attacks with possibly some lymphangitis for several years. However in highly endemic areas this period is frequently much shorter and recently from the South Pacific cases have been reported in which the incubation period was apparently only three and a half months lymphangitis of the arm and of the spermatic cord was associated with fever and the finding of the adult worms but not of microfilariæ

A **Symptomless infection**—In most endemic areas the majority of the infections are symptomless and in the areas of low and moderate endemicity they remain so indefinitely However as fresh infections are superimposed on account either of sheer weight of numbers of adult worms

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The word latent is avoided here because it is often used as an antonym to patent and these infections are certainly patent to anyone who examines the blood at the appropriate time further, the word also seems to suggest that at any time the worm or worms causing this infection may suddenly be stirred into activity and the infection may then flare up into clinically patent on this probably very seldom occurs

or of developing intolerance on the part of the host some of these subjects will later develop symptoms and naturally the numbers of such persons will vary in direct proportion to the intensity of the infection to which they are subjected (*vide supra*)

B Lymphangitis and lymphadenitis —(i) Uncomplicated Attacks may occur at frequent and often regular intervals it is commonly noted by patients that the attacks recur always at some particular phase of the moon, or in women at one particular state of the menstrual cycle. The whole limb and the glands in particular are very painful, and often a red line can be seen running up the limb in the upper limb the epitrochlear is most commonly involved The skin over the lymphatic vessels is red and œdematous and the whole limb may be slightly swollen Painful subcutaneous nodules fixed to the skin will also appear in about 10 per cent of cases The site of the adult worm may be indicated by a particularly red and tender spot.

The local symptoms are usually accompanied by a febrile attack, temperature 100 F to 102 F, with general malaise, headaches and pains all over the body that usually lasts for two or three days The local symptoms may subside after four or five days.

Not infrequently the general symptoms appear without any definite localising symptoms and conversely local signs may be unaccompanied by fever

(ii) If sepsis either hæmatogenous or otherwise, is added the local and general symptoms will be of a more severe nature the whole limb being very swollen and red and the temperature running up to 104 F or 105 F daily for a week or more When such an attack subsides the limb seldom returns to its previous diameter

(iii) A local abscess at the site of the dead worm may be left.

C. Elephantiasis —After the first few attacks of uncomplicated lymphangitis the limb may return to its previous size but in course of time each attack leads to a slight permanent increase in the size of the limb and in some cases the increase is insidious and occurs independently of patent attacks of lymphangitis At first there is ordinary pitting œdema then the swelling becomes harder and does not pit later the whole limb becomes massive brawny harsh and dry and folds and/or cracks appear and finally these become infected with septic organisms and ulceration occurs These changes take place most commonly in the arms forearms and hands legs and feet (plate XXIII figures 4 to 6) scrotum (plate XXII figures 1 to 3 and plate XXIII figures 5 and 6) penis (plate XXIII figure 6) and labia and occasionally in the mammæ

The bizarre deformities that filarial infection will produce are well known they are capitalized in the East by beggars who parade them for the purpose of obtaining alms and in the West by writers of textbooks who always seek the most extreme examples for decorating their pages Elephantiasis is simply the effect of lymphatic obstruction and may occur in non filarial subjects, but no condition produces such effective obstruction as filariasis and in a filaria-endemic area all cases of elephantiasis may be accepted as filarial in origin unless there is strong evidence to the contrary

D Lymph varix —Varices will occur mainly when the vessels lie superficially or in loose cellular tissue and are therefore relatively unsupported Lymph varix may thus be found on the surface of a limb, or in the groin in the spermatic cord in the scrotum or in the deep abdominal lymphatics in the bladder wall, or around the kidney

They may be (i) uncomplicated or (ii) the varix may rupture (a) to the surface in the groin or scrotum, producing lymphorrhœa (b) into a joint *e g* knee or hip causing filarial synovitis (c) into the tunica causing

a lymphocele (hydrocele) (d) into the urinary bladder or the kidney pelvis or calices causing lymphuria or (e) into the peritoneum causing ascites A characteristic of lymph varices is their sudden disappearance and reappearance within a few days Otherwise these conditions are mostly self explanatory two only appear to need further description

(a) The **lymphorrhœa** produced when a superficial lymph varix in the groin or in the scrotum ruptures or when an ill advised surgical operation is undertaken is very troublesome there is continuous oozing from the part that may amount to seven or eight ounces of lymph in 24 hours and this keeps the patient's clothes continuously wet

(b) The onset of **lymphuria** is often insidious but is at other times associated with an aching pain in the bladder or the loin or in both dysuria and the passage of clots There is albumin in the urine and many lymphocytes but except for the possible presence of clots the gross appearance of the urine is little changed

(iii) The complications caused by hæmorrhage into the cord tunica or urinary tract being dependent mainly on trauma are likely to be intermittent. The conditions will alternate with simple leakage of lymph or chyle in the various localities

(ii) The most serious of the septic complications is acute funiculitis and epididymo-orchitis which often leads to peritonitis and septicæmia the infection is usually streptococcal and appears to be hæmatogenous in origin in the majority of cases The severe general condition is out of all proportion to the local signs and the onset is that of an acute abdominal emergency It may occur in a patient who has had a lymph varix or lymphuria for some time or it may appear as an early even if not the first symptom These septic complications are even more likely to occur in cases of chyluria where the original source of septic infection may be the intestinal tract (*vide infra*)

E. **Chyle varix**—(i) Chyle varix is probably less frequently uncomplicated and symptomless than is the corresponding lymph condition but it also may be uncomplicated The condition will usually cause a certain amount of abdominal discomfort backache or pain in the loin.

(ii) and (iii) (a) *Chylocele* is also less common than lymphocele but does frequently occur The swelling will not transmit light and is very likely to be complicated by a certain amount of hæmorrhage (*hæmato chylocele*), it might therefore be mistaken for a strangulated hernia if not carefully examined

(b) *Chyluria* on the other hand is more common than lymphuria Attention is usually drawn to the condition by the patient's noticing that his or her urine is milky but it may be preceded by back pain and aching in the pelvis and loin in women the onset of chyluria or hæmatochyluria may follow childbirth and in men any form of physical strain. A very troublesome complication is urinary retention due to the presence of clots in the bladder that periodically block the urethra In the case of kidney chyluria the clots may block the ureters temporarily it is seldom that there is clinical evidence of this but occasionally there will be typical renal colic

An excretion pyelogram will often show some dilatation of the ureters and during cystoscopy it is not uncommon to see the clot being slowly extruded from the ureteric orifice In about three-quarters of the cases the dilated lymph vessels can be seen usually just above the ureteric bar but sometimes lower in the trigone

The chyluric attack usually lasts about a week or ten days, and then clears up entirely for some months but sometimes it will last for several weeks and in rare cases even for months The general symptom

associated with the attack seldom amount to more than lassitude (if attack is a short one) and debility (if it is longer) but the psychologi effect may be quite serious and the fact that strain is likely to bring an attack will prevent the patient from leading a normal life

(c) **Chylous ascites** will not be distinguished clinically from ordin filarial ascites due to the rupture of a lymph varix but will be appar when paracentesis is performed septic complications are more likely occur than in the simple ascites and in this case the picture will be of peritonitis.

(d) **Chylous diarrhoea** resulting from the reflux of chyle into intestinal canal has been reported but is apparently a rare filarial ma festation

(iv) **Suppurating**.—It will not be necessary to discuss the sep complications that may be associated with any one of these ruptures chyle varices but in view of the closer association with the intestin canal they are likely to be commoner than in the case of lymph varic as has been indicated above

F **General symptoms**.—(i) Fever The fever that develops filariasis is due either (i) to the worm and/or its metabolites entire independently of secondary infection, and for this the accepted expressi 'filarial fever' is quite appropriate or (ii) to secondary infection of t blocked lymphatic channels of the elephantoid skin or of the varices a for this the expression secondary fever to which the words of filarias might be added if the context did not already make it clear seems to unobjectionable *

(ii) **Allergic manifestations**.—There is undoubtedly a form of urticar that is associated with a filarial attack and often recurs at regular interva Similarly the easiest explanation for the frequent cord and testicul swellings that occur even when the demonstrable filarial lesions are other parts of the body is on the basis of local allergic response This ma be a specific tropism as suggested by Michael (1944) but is in the writer opinion more probably the result of previous local sensitization b migrating filariae

With regard to asthma one is on less certain ground but man filarial subjects with asthma give a history of periodic attacks that cann be correlated with the season or with any change in the patient's enviro ment or habits which may or may not be accompanied by local filari manifestations The writer can give no statistical data in support of th clinical impression

G **Psychoneurotic manifestations**.—The psychoneurotic effects wer very apparent in young white and Anglo-Indian girls who living in th poorest parts of certain Indian towns—Calcutta for example—in clo association with the native population frequently became infected wit filaria but actually seldom developed any gross deformities on accoun of the lightness of the infections However the psychoneurotic poten tialities of filarial infection were probably never fully appreciated unt very recently when a large number of members of United States fightin forces were heavily infected in a South Pacific island The combinatio of (a) the frequent genital location of the lesions (b) occasional asso ciated venereal disease (c) the frequent deformities in the natives wit

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* The fever that occurs when elephantoid skin and tissue become infected ha been called elephantoid fever Not only is the expression elephantoid fever a example of ridiculously misapplied adjective but it is misleading as the fever th develops when secondary infection occurs in other filarial conditions such as lymph o chyle varices, has exactly the same aetiology, and the expression elephantoid fever applied in these cases would be even more ridiculous.

whom they associated (d) the alarming pictures in medical textbo[oks] to whose influence they were too often directly and indirec[tly] subjected and (e) the ill advised publicity given to the whole incide[nt] led to the development of psychoneurosis in a very large percentage [of] those with even the mildest somatic lesion It has been estimated t[hat] 90 per cent of the disability of the personnel invalided on account of t[he] infection were of psychoneurotic origin.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

This must be considered under a number of headings —

(a) Duration of residence in an endemic area —The time taken [for] the development of filarial lesions varies in different localities (*vide supr[a]*) a diagnosis of filariasis at an earlier date should be made with considera[ble] caution, but, as there are exceptions to the general rule it is also danger[ous] to rule out filariasis entirely on these grounds alone

(b) *History of a previous attack.*—A history of previous attacks [of] lymphangitis without any apparent local cause followed by œdema of [the] limb that does not always subside and associated with a mild or sev[ere] febrile attack should arouse great suspicion Periodic febrile attacks al[one] in cases in which malaria can be excluded are also suggestive

(c) Clinical picture —The acute painful descending lymphangitis [and] lymphadenitis with fever should always be viewed with suspicion in [an] endemic area but they may have other causes the lymph varix braw[ny] œdema and elephantiasis of the limbs genitalia or breasts will be m[ore] characteristic but are only evidence of lymphatic obstruction—the m[ost] common cause of which in the endemic areas is of course filariasis—[and] not *per se* of filariasis itself and certain other lesions that commonly oc[cur] in filariasis such as hydrocele are as likely to have some other cause e[ven] in endemic areas

When hypertrophy occurs in other regions where there is a go[od] collateral lymph supply *e g* the head or face back or buttock it [will] seldom if ever be due to filariasis and such conditions as diffuse fib[ro]matosis fibro-lipoma and von Recklinghausen s disease should be co[n]sidered Œdema due to other common causes such as cardiac and re[nal] diseases is usually bilateral but angioneurotic œdema like filariasis [will] usually be unilateral Too much weight should not be placed on [the] non pitting character of filarial œdema as it takes some time for the fibr[otic] changes to occur Hypopituitrism may also produce a condition suggest[ive] of filariasis, but the excess tissue will have a different character as w[ell] as being bilateral

(d) Laboratory examinations.—(i) Blood The examination of [the] blood for microfilariæ has its strict limitations as a means of diagnos[ing] filarial disease see p 634 for correlation between filarial infection [and] filarial disease

Summarizing these observations one can say that the finding [of] microfilariæ indicates filarial infection but not necessarily filarial disea[se] failure to find them does not exclude either filarial infection or fila[rial] disease

In countries where the infection is transmitted by *Culex fatigans* [or] other night biting mosquitoes and the microfilaria show nocturnal peri[od]icity the blood for examination must be taken between 10 o clock [at] night and 2 o clock in the morning whereas in other countries such [as] Fiji where it is transmitted by a diurnal biter the blood should be ta[ken] at about 10 o clock in the morning

Technique—Take about 20 c.mm of blood preferably an accurately m[easured] quantity, into a hæmoglobinometer pipett from the finger r ear and m[ake] a thick film on a perfectly clean slid Allow it to dry then stain and dehæ[moglobinize]

globinize with dilute Giemsa's stain Pour off the stain very carefully—do not wash it off Dry the film in air and examine with a low-power lens. The number of microfilariæ will vary from one in many films to hundreds in one film by multiplying the number per thick smear by 50, the number per c.cm will be arrived at.

It will sometimes be worth employing a concentration method. Take 5 c.cm. of blood from a vein with a serum syringe into a centrifuge tube containing 10 c.cm of distilled water mix thoroughly until the blood is laked, place two or three threads of cotton-wool in the centrifuge tube centrifuge for 5 minutes with a hand or an electric centrifuge pour off the supernatant fluid pick up the threads with a *rough* straight piece of wire and examine the sediment with the low-power objective Microfilariæ if present will be seen entangled in the cotton threads.

No assistance will be obtained from the blood count. Eosinophilia, though frequently present is too inconstant a finding to be of either positive or negative value

(ii) Immunological tests.—A complement fixation test in which the antigen is prepared from the dog filaria *Dirofilaria immitis* has proved successful but apparently is dependent on the worm being alive.

The simpler intradermal test has been used more widely but there is considerable variation in the technique used. A 1 in 8,000 *Dirofilaria* antigen with 0.3 per cent phenol of which 0 01 c cm. is given by means of a tuberculin syringe, gives a minimum of false positive reactions even in allergic individuals. A weal of at least 1 c cm. in diameter will indicate a positive reaction. A H Hamilton (personal communication), basing his opinion on experience in the East Indies considers that positive intradermal tests with *dirofilaria* antigen are of little value since about two out of three normal natives will show positive results. A negative test however he considers to be of the greatest value as excluding filarial infection.

These intradermal tests for which a really satisfactory standard technique has still to be found indicate rather the reactivity of the host than the presence of the worms. Their particular usefulness will not be in a highly endemic area but to diagnose an obscure lymphangitis in a patient who has at one time been in an endemic area but shows no microfilariæ in the blood

A flocculation test with hydrocele fluid has a limited usefulness

(iii) Urine —The milky urine in chyluria can be identified with the naked eye For this method of examination for filaria *see* p 640 above

(e) Other procedures —These include cystoscopy and pyelography to identify the sites of the ruptured lymph varices in chyluria, roentgenography to show the presence of calcified filariæ and gland biopsy to identify the adult worm.

PREVENTION

This must be considered under two headings —

A The prevention of the spread of infection

B The prevention of attacks in those already infected

A. The prevention of the spread of infection —The reader should refer back to p 636 where the essentials for transmission and the factors concerned in endemicity are discussed. These are —

(i) The source of infection microfilariæ in the peripheral blood of man.
(ii) The vector mosquito
(iii) Susceptible man.
(iv) The links between (i) and (ii) and (ii) and (iii)

This aspect of prevention can be discussed shortly under each of these four headings.

(i) Man is the only source of microfilariæ but in highly endemic areas a very large percentage of the community will have them in their blood Further there is no drug that has more than a very temporary effect on

the microfilariæ in the blood Therefore any attempt at wholesale sterilization of infected individual is at present out of the question

Segregation of infected communities should as far as possible be practised This may be advisable when labour forces police or armies are recruited from endemic areas and are to be employed in areas where transmission is possible.

Again the circumstances might be such that it would be advisable to weed out altogether those who had microfilariæ in their blood. If this were decided upon it would be advisable to examine several night blood specimens from each individual

In endemic areas the highest infection rate is amongst the poorer classes of people who have made no attempt to protect themselves from *mosquito bites so that the uninfected should build their houses* well away from poor class dwellings and should see that any servants that are allowed to sleep in their houses are free from infection

(ii) Control of the transmitting mosquito will provide the most promising line of attack While at least a dozen species belonging to four genera *Culex Aedes Mansonioides* and *Anopheles* have been found infected in nature and many others have been infected experimentally *Culex fatigans* is the predominant transmitter in India and in many other tropical countries It is a night feeder a breeder in dirty and stagnant water and is comparatively local in its habits it is not therefore very difficult to control around dwellings by the usual measures directed against either larvæ or adults When it is ascertained that some other species is the main transmitter in any locality special measures must be directed against that species The subject of mosquito control is beyond the scope of this book, but some further references to anti mosquito measures will be found on pages 113 to 117

(iii) There is nothing to be said under this heading as there is little evidence that there is any individual immunity to *infection* and there is certainly no evidence that it is possible to induce or increase such immunity

(iv) In institutions or even in households infected persons must be kept in mosquito-proof rooms or at least under mosquito nets at night in order to prevent infection of the local mosquitoes

Conversely for personal protection in mosquito-ridden endemic areas screening mosquito nets suitable clothing and repellents should always be used as a precaution against being bitten by infected mosquitoes

B *The prevention of attacks in those already infected.*—The most important measure is the removal of any septic focus that might through the blood give rise to infection at the site of a dead worm or in tissue otherwise damaged by filarial metabolites This may be an external one *e g* a tinea infection or dermatitis or an internal one *e g* pyorrhœa an apical abscess septic tonsils sinuses gall bladder cervix prostate or urinary tract or a bowel lesion such as chronic amœbiasis or a *Shigella* infection Elimination of such a focus *e g* of a sub-clinical amœbic infection by a course of carbarsone or diodoquin will often reduce appreciably the number of febrile attacks that a patient suffers

This precaution should be taken in all infected persons whether they have suffered previous attacks or not

However as well as by removing septic foci persons who have already had attacks of filarial lymphangitis or some other filarial syndrome can reduce considerably the chances of further attacks by maintaining good general health and if possible moving to a cooler climate A recommendation to this effect usually can be made with a clear conscience as *even if such persons have microfilariæ in their blood and there are Culex fatigans* or other vectors in the locality they will not be a source of danger

to the new community amongst whom they go to live, provided the temperature and humidity are outside the ranges within which transmission occurs (*vide supra*) It is however, quite unnecessary to recommend such a measure as transfer to a cold climate for an infected person who has suffered no clinical attacks except of course as a means of preventing infection

TREATMENT

Introduction—The treatment of this condition is more unsatisfactory than that of almost any other tropical disease but partly because of this and also because of the variety of the clinical conditions that occur in filarial infection, a very great deal has been written on it. It is proposed to treat the subject summarily here It can best be considered under the following headings —

A. Specific treatment
B Treatment of secondary infections
C The relief of lymphatic obstruction
D Palliative treatment for special conditions

A *Specific treatment*—No true specific has yet been found but there does not seem to be any valid reason why at some future date one should not be expected. Some drugs when given intravenously appear to destroy the microfilariæ but this does nothing towards helping the patient for the adult worm, which is not in the blood stream is left intact. When the adult worm has once settled in the tissues it is difficult to reach it. The best method would be to inject some drug that is absorbed by the lymphatics distally to the worm so that it would get behind it, so to speak, or in the case of chyluria and other syndromes following chyle varix a drug that would be absorbed from the intestinal tract into the lacteals. It has been suggested that it would be dangerous to destroy all the worms *in situ* at one time it might certainly cause a sharp reaction in heavily infected cases but should we find such a drug it would probably not be very difficult to temper the treatment to the heavily infected

Antimonyl tartrates were used by Rogers in 1917 but it was shown that these compounds had no effect on the microfilariæ although they had certain beneficial results on the pathological lesions produced by the parasite. Various other drugs have been suggested from time to time. The Filariasis Commission of the London School of Tropical Medicine working in British Guiana in 1921 experimented with many preparations but without success Systematic clinical experiments with various drugs have been carried out by Rao at the Calcutta School of Tropical Medicine during the last 20 years Patients at various stages of the infection were treated by drugs whose therapeutic efficiency in other parasitic infection was known. The results may be briefly stated —

Of the organo-metallic compounds soamin (atoxyl) appears to be most satisfactory in controlling the symptoms in the early stages It can be given subcutaneously intramuscularly or intravenously and is usually non toxic although a few exceptionally susceptible persons who exhibit toxic symptoms even after the first injection have been encountered. There does not appear to be any appreciable reduction in the microfilaria count, even after a full course of treatment with this drug, but in many cases the patients have remained free from fever and lymphangitis for a long time after treatment with soamin. Certain other arsenic compounds such as tryparsamide novarsenobillon and sulfarsenol, have given almost as satisfactory results as soamin tryparsamide given in 2 to 3 gramme doses intravenously appeared to control the symptoms in chyluria in particular

Practically all available organic compounds containing antimony were investigated. Of these the trivalent compound Fouadin gave the most satisfactory results. The drug can be administered subcutaneously, intramuscularly or intravenously and is non-toxic. The effect of the drug on the filarial parasite seems to be temporary as the microfilariæ reappear in the blood after the lapse of some days though it may be several weeks before they reach their previous level. This drug usually controls the inflammation and fever for a considerable time.

A recent addition to the antimony drugs used in this disease is anthiomaline—lithium antimony thiomalate. Some workers have claimed good results in reducing the microfilaria counts for several months at least. It is given intramuscularly in doses of 2 c cm to 4 c cm of a 6 per cent solution according to the patient's tolerance on alternate days up to 10 doses.

Several vegetable drugs which are reported to be efficacious in allied helminthic infection were administered orally and in some cases by injection. Oil of chenopodium appeared to give satisfactory results in some cases; when given intramuscularly it reduced the number of embryos in the circulation and controlled the attacks of lymphangitis but the injections caused painful reactions.

B. Treatment of secondary infections.—This should be considered under the headings:—

(i) Local treatment.
(ii) General chemotherapeutic treatment.
(iii) Vaccine treatment.
(iv) The search for and eradication of septic foci.

(i) Local treatment will naturally depend largely on the part affected and the nature of the lesions. Ulcers on an elephantoid leg will in some cases be benefited by elevation of the limb followed by the application of powdered sulphonamide to the ulcerated area and tight strapping of the whole affected part of the limb with elastoplast or some similar material which must be left for several days.

For lymphangitis and lymphadenitis whether there is secondary infection or not, hot fomentations and local application of heat by the infra-red lamp will relieve the pain and reduce the inflammation.

(ii) Of the general chemotherapeutic agents the new 'sulpha' drugs have proved very useful in the treatment of secondary infections of all kinds and very satisfactory results have been obtained in the treatment of such very serious conditions as epididymo-orchitis and funiculitis by the administration of red prontosil. Sulphapyridine and sulphathiazole have also proved very effective but it is probable that new and more effective anti-streptococcal drugs, *e g* penicillin, will be in general use by the time this chapter is printed.

(iii) Vaccines have been the mainstay in the treatment of many filarial lesions for some time and it seems doubtful if the good effects claimed and in some cases undoubtedly produced, can be attributed to the specific action of the vaccines on the secondary infection. The effect has probably been that of non-specific protein therapy in many cases. This has obviously been the line of thought of some workers who have used typhoid vaccines or milk injections.

A vaccine, consisting of 10 million hæmolytic streptococci of many strains and 50 million staphylococci of several strains of *aureus* and *albus* has been used by Rao at the Calcutta School of Tropical Medicine over a period of 15 years in more than 50 000 cases. The vaccine is given intracutaneously in doses of 0.02 c cm to 0.1 c cm twice weekly up to a total of 15 to 20 injections. The ameliorative effects have been sufficiently

The female worm measures 55 mm. in length with a diameter of 0 16 mm The mouth is terminal without appendages or lips The vulval opening is 0.98 mm from the tip of the tail The general course of the uterus and its branches ending in ovaries is practically the same as in the female of *Wuchereria bancrofti*

The ovum varies greatly in size measuring 0 027 mm. long and 0 018 mm broad.

The average length of the embryo in the fresh state is 263 microns while in smear preparations it is 186 microns (177 to 230 microns) The most distinctive character in the embryo of this species is the presence of two discrete nuclei at the tip of the tail

The adult *Wuchereria malayi* lives in the lymphatics of the extremities in man and the sheathed embryos circulate in the blood showing a nocturnal periodicity

Intermediate hosts.—The chief transmitters of the parasite are *Taeniorhynchus (Mansonioides) annulifera* *T (Mansonioides) uniformis* and *T (Mansonioides) indiana* (India and Malaya) *T (Mansonioides) longipalpis* (Malaya) *Anopheles barbirostris* (Celebes) and *Anopheles hyrcanus* var *sinensis* (China), other potential transmitters are *Anopheles hyrcanus* var *nigerrimus* *Armigeres obturbans* In India *Taeniorhynchus* spp breed on the common water plant *Pistia stratiotes* found in ponds and tanks (Iyengar 1935) while in Assam they breed also on the water hyacinth and *dol* grass (Fraser 1938) and in Malaya in mangrove swamps

Symptomatology —The pathological lesions produced by this parasite consist of lymphatic obstruction of the extremities only Periodical inflammatory attacks of the lymphatic vessels and glands occasionally ending in abscesses are common. No case of genital affection of hydrocele, or of chyluria due to this parasite has so far been reported.

Prevention —This consists in anti mosquito measures and in the prevention of bites by infected mosquitoes In North Travancore, Sweet and Pillai (1937) have reported successful results in the eradication of *Wuchereria malayi* infection by a periodical hand removal of the *Pistia* plants from the ponds, but as in some localities at least it can live on other plants (Fraser *loc cit.*) this method may prove disappointing.

Treatment.—No specific is known The treatment of the acute and chronic stages of the diseases produced by these parasites is on the same lines as in the case of infection with *Wuchereria bancrofti*

FILARIASIS DUE TO *LOA LOA*

Definition —Loaiasis or *Loa loa* infection is caused by the filarioid worm, *Loa loa* (Cobbold, 1896) a parasite that wanders in the subcutaneous tissue giving rise to fugitive swellings (Calabar swellings) and to a local reaction in the eye when they pass under the conjunctiva The intermediate hosts are certain tabanid flies of the genus *Chrysops* which transmit the infection to man by their bite

Geographical distribution —It has a wide distribution in West and Central Africa particularly along the river Congo and its tributaries. A parasite of the same genus was reported by Maplestone (1938) from India he gave it the name *Loa inquirenda* provisionally

The parasite.—The average length of the male is 30 mm. to 34 mm. and the breadth about 0 4 mm. The cuticle is embossed with protuberances. The female varies in length from 50 mm to 70 mm. and is about 0.5 mm. broad The microfilaria is the same length as that of *Wuchereria bancrofti* and has a sheath.

The microfilariæ exhibit diurnal periodicity and are transmitted by *Chrysops dimidiata* and *Chrysops silacea*.

The infective third stage larvæ appear at the proboscis of these flies in about ten days but their growth to the adult stage in man is believed to take several years and they may live for up to 15 years

The baboon also acts as a host to this infection

Symptomatology —Generally the worm infection does not give rise to any signs or symptoms However in some cases fugitive swellings as large as a hen's egg known as Calabar swellings occur on the course of the worm's migrations The worms migrate in the arms across the bridge of the nose, across the eyeball under the conjunctiva, or in any other part of the body The swellings are hot tender and painful they last for a few days or weeks and then disappear suddenly and they are probably allergic in nature.

Other signs and symptoms of disease produced by this parasite are urticaria hydrocele lymphatic œdema and abscess

Prevention —This consists in personal protection from the bites of tabanid flies and measures to control these flies.

Treatment.—No drug so far used has any lethal effect on the parasite in the human system. Cold applications of sedative lotions and com presses relieve the pain The annoying migrations of the worm may be cut short by surgical removal as they come near to the surface when they cross the bridge of the nose this is a convenient place to catch them

ONCHOCERCIASIS

Definition —Onchocerciasis or infection by the helminthic parasite *Onchocercus volvulus* (Leuckart, 1893) is characterized by tumours in the subcutaneous tissues which appear in different parts of the body it is transmitted from man to man by a gnat (Simulium) The condition is found in a wide area in tropical Africa from Senegal to the Belgian Congo, as far east as the Sudan and Kenya Colony and in circumscribed areas in southern Mexico and Guatemala. In Guatemala the infection is chiefly found in coffee plantations on the Pacific slopes of Guatemala at elevations between 1,800 and 6 000 feet The parasite found in Guatemala has been given the name *Onchocercus cæcutiens* (Brumpt 1919) but it is now believed to be identical with *Onchocercus volvulus*

The parasite.—The male adult is 20 mm. to 40 mm. long and 0.2 mm broad the tail is bulbous at the tip and terminates in a single spiral turn. The female is 60 mm to 70 mm. long and 0 4 mm. broad and ovoviviparous the egg has a peculiarly striated shell with a pointed process at each pole The microfilaria is sheathless it measures 300 microns long and 8 microns broad

Intermediate hosts.—The embryos undergo development in the thoracic muscles of a *Simulium* fly in the same manner as those of *Wuchereria bancrofti* in *Culex fatigans* The species in Africa is *Simulium damnosum* and in Guatemala *Simulium avidum Simulium ochraceum* and *Simulium mooseri*. These flies breed in swiftly moving streams the larvæ attach themselves to stems twigs and leaves of plant on the banks floating on the water The infection is most common in adult males, but tumours have been reported in children even as young as two months.

Symptomatology —*Onchocercus volvulus* produces tumours of the skin varying in size from a pea to a hen s egg These firm fibrous tumours give rise to considerable pain in the early stages but only rarely break down and form abscesses They are particularly painful when they occur near the joints In aged patients they are reported to form the

starting point of neoplasms Lymphatic obstruction of the scrotum, formation of hydrocele enlargement of testes and abscess formation produced by the worm have been recorded An allergic dermatitis may occur and patients sometimes complain of pruritus

The nodules vary in number from one or two up to 150 but in most endemic areas there are seldom more than five or six in one individual. The number of lesions apparently depends on the degree of the infection in the locality of endemicity the number of naturally infected flies may vary from about 5 per cent to 33 per cent in highly endemic areas.

In Africa, 95 per cent of the nodules are in parts of the body other than the head but in Guatemala the distribution is reversed and most nodules appear on the head

There are instances in which the worms are present in the tissues without producing clinical nodules.

When the lesions occur on the head epileptiform convulsions due to erosion of the cranium by the tumours of the periosteum have been reported.

Eye lesions—*Photophobia discomfort and irritation associated with* conjunctivitis, epiphora and amblyopia may precede other visible changes, and punctate keratitis and inflammation of the iris ciliary body and *choroid may follow Microfilariæ may eventually invade the optic nerve* and cause blindness. The eye changes are also thought to be toxic or allergic in nature and due to metabolites produced by the worm in other *parts of the body, as they are sometimes unassociated with the actual* presence of the microfilariæ in the eye Further, the changes are more pronounced in persons on a poor diet.

Blood picture—*A very high eosinophilia is the rule counts of 20 to* 75 per cent of the total leucocytes have been reported in Guatemala and Mexico

Treatment.—*Excision of the tumours as they appear* is the best means of avoiding subsequent complications Fouadin (*see* p 649) appears to have some effect on the lesions and good results have been claimed from *the injection of a 0.1 per cent solution of plasmochin* into the anterior chamber of the eye.

Prevention—Measures against *Simulium* have not been very successful and Strong believes that an extensive nodule-removal campaign that reduces the local reservoir of infection is the most profitable preventive measure.

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DRACONTIASIS, OR GUINEA WORM DISEASE

by

L. Everard Napier and S. Sundar Rao

Paulus Aeginus wrote stating that in India and Egypt a class of worms called dracunculi formed in the muscular parts of the body and moved under the skin, and that after a time the skin opened and the head came out. Avicenna, the Arabian physician, named the worm *vena medina*, as it was common in Medina.

Our present knowledge about the spread of this infection dates from 1869, when Fedschenko, a Russian biologist in Turkestan, showed that the embryo of *Dracunculus medinensis* undergoes developmental changes in cyclops. He observed the infected cyclops up to the fourth week and stated that the embryo completed its metamorphosis on the twelfth day. Fedschenko's observation which incidentally initiated a new principle in medicine was subsequently confirmed by other workers, including Manson who in 1893 repeated the experiments in London, and found that the ecdysis of the guinea-worm embryo in the local cyclopide took place in the sixth week. Leiper working in Africa in 1907 added further confirmation and produced the disease experimentally in monkeys.

In 1913, Liston, Turkhud and Bhave extended this work further and demonstrated at the Haffkine Institute, Bombay that a man who drank water containing infected cyclops developed the worm in 348 days.

Geographical distribution.—Guinea worm disease is widely distributed in the tropics. It occurs in Asia, Africa and South America.

In Asia it is found in certain parts of India, Iran, Arabia and Turkestan and South East Russia, in Africa, in the Nile Valley in the Anglo-Egyptian Sudan, in Uganda, in Lake Chad district and Bornu, and on the West Coast, and in South America in the Caribbean Islands and in British Guiana and Brazil.

In India, the infection is confined principally to the western half of the peninsula. It occurs extensively in the Bombay Presidency except in some coastal areas south of Bombay City, in the Nizam of Hyderabad's Dominions, in the Madras Presidency, in Rajputana (except the desert areas) and Central India, in the east part of the Central Provinces, in the North West Frontier Province, in Jammu district of Kashmir and in certain parts of the Punjab.

The disease does not occur at all in the north-east part of India, namely, in Bengal, Assam and the adjoining provinces, nor in Ceylon, Malaya or the East Indies (except possibly in some localities in the Dutch East Indies), Australasia, China or the Pacific Islands. Nor has it been reported from Europe or North America.

ÆTIOLOGY

Morphology of the parasite.—A fully grown female worm is 32 cm. to 120 cm. (12 to 48 inches) long and 1.5 mm. to 1.7 mm. (about 1/16 inch) in diameter. The worm is round, smooth and milky white in colour. The head end is tapering and rounded. The tail, also tapering, is curved like a hook. The mature worm is packed with embryos from head to tail; there are about three million embryos in each worm.

The male worm apparently measures from 12 mm. to 40 mm. long and 0.4 mm. broad, but few specimens have been seen and these have mostly come from experimentally infected animals.

Embryos are 0.5 mm. to 0.75 mm. long (1/42 inch). They have a flattened body and a tapering tail. They lie coiled up on discharge from the worm, but they soon stretch out in water and begin to swim vigorously with a tadpole-like motion. They can live in clean water for a week and much longer in muddy water. There is no further development of the embryos until they enter the cyclops.

Cycle.—While in water the embryos (first stage larvæ) are swallowed by the cyclops (as many as ten may be seen in one cyclops), and migrate to the body cavity where they undergo further development; at the end of the fifth day the embryos lose their tapering tails; they moult on the 9th day, develop a bilobed tail and grow much longer (*see* plate XXIV).

All these changes take about two weeks in the summer months There is no further growth inside the cyclops

When infected cyclops are swallowed by man in drinking water they are killed by the gastric juice in the stomach The larvæ which were sluggish hitherto become very active and escape from the dead cyclops they pierce the intestinal wall and reach the loose retroperitoneal tissue where they develop further and then migrate to other parts of the body of their definitive host The full development to the mature adult stage takes between eight months and one year

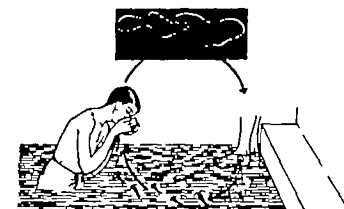


Figure 160 Showing the cycle of infection from man to man through the fresh-water cyclops.

When the female becomes gravid it migrates to the surface of the body usually to those parts that are most likely to come in contact with water *e.g* legs and feet When the worm reaches the site of choice, it secretes some irritant material which amongst other things causes a local reaction with the formation of a blister Eventually when it comes in contact with water the blister breaks and the uterus prolapses through the mouth or through a rupture in the body wall of the worm appears at the mouth of the opening bursts and discharges a milky fluid swarming with larvæ These pass into the water where they may live free up to about a week after which they die unless in the meantime they are swallowed by the cyclops present in the water when the whole cycle may be repeated

The discharge of larvæ is determined by temperature in nature by contact with cold water but it can be precipitated by the application of a piece of ice or an ethyl-chloride spray The migration of the adult worm may also be determined by thermotaxis as in Rajputana where *bhistis* (water-carriers) carry water in leather bags on their backs and worms often appear on the back. In the people who carry water in pots on their shoulders or head the worm may appear on the neck or even on the head itself

Whilst there is no evidence that man ever enjoys complete immunity from invasion by this worm there is evidence from human experiments in Bombay in which volunteers were fed large numbers of infected cyclops and only one developed a single worm and from numerous animal experiments that only a small percentage of the larvæ ingested by man reach maturity

Intermediate host (cyclops) —Cyclopidæ are present in most collections of fresh water and are found throughout the year They breed actively in the summer they are fairly abundant in the rainy season (July through September), and they decrease slightly in the winter months. They have a pear shaped symmetrical body with a forked tail two pairs of antennæ five pairs of swimming legs, and one eye They measure about a twelfth of an inch and are just visible to the naked eye There are about six species of cyclopidæ in India They are —

Mesocyclops leuckarti	*Mesocyclops* *uncens*
hyalinus	*Paracyclops fimbriatus* and
decipiens	*Microcyclops k rvei*

Other species of cyclopidæ in which development may take place include *coronatus magnus, prasinus, serrulatus, quadricornis strenuus vernalis, viridis* and *vermifer*. All of these feed readily upon the guinea worm larvæ.

Cyclops thus infected do not live as long as uninfected ones but they have been found to live up to two months. The average life of cyclops is about three months but this period is considerably affected by the temperature of the water, and its acidity or alkalinity: they die when the water is warmed to a temperature of 60° C.

EPIDEMIOLOGY AND FACTORS IN TRANSMISSION

It will be seen from the above description of the transmission cycle that three conditions are necessary, namely (i) contamination of the water supply with larvæ by the definitive host, man, (ii) the presence of suitable *cyclops in the water-supply to act as intermediate host*, and (iii) consumption by a susceptible host of the water contaminated with infected cyclops. The conditions necessary for the disease to become endemic are therefore:—

(a) a very special set of social and sanitary circumstances in which man, firstly steps barefooted into the water when taking water for drinking or other purposes (theoretically man might contaminate the water by the immersion of other parts, and other animals might act as definitive hosts) and secondly drinks the water from this source without filtration or boiling,

(b) a water source in which cyclops will live and multiply,

(c) the actual presence of cyclops of certain species in sufficient numbers in this water, and

(d) the commencement of the cycle by the introduction of an infected person into the community.

We will consider each of these conditions in association with known facts regarding the epidemiology of the disease.

(a) Special social and sanitary circumstances.—Dracontiasis is known to be limited in its distribution to towns and villages where such conditions exist.

The water-supply of a large number of villages in tropical and subtropical countries is from *tanks* (*i.e.* reservoirs) or *step-wells*. At several points around the tank are stone, brick or concrete steps that extend into the tank two or three feet below the water level. It is the local practice to walk down these steps into the water in order to fill the water pot conveniently, even if the tank is reserved for drinking water which is not always the case. In fact, in many instances the villager will first wash himself and his clothes, then wash out his mouth with the water and drink some and finally fill his or her water pot. The step-well is a large shallow well with steps leading down to and into the water as in the case of the tank.

This disease does not occur in towns where there is a pipe-borne water supply from a protected source or in villages where parapeted draw wells, pump-wells, or tube wells are used exclusively. Further the disease has disappeared from towns and villages when the water-supply has been changed from the former to the latter type.

The type of water-supply in use is often not a matter of free choice for the community but is determined by soil and climatic conditions; for example in very dry countries all natural water supply must of necessity be from deep wells, and the disease does not occur.

Finally, *educated individuals* who have taken the precaution of boiling or filtering their drinking water from these sources have avoided the disease.

(b) Suitable water supply.—Cyclopidæ are bottom feeders and do not flourish in deep wells; they require a certain amount of organic matter for their food; they are susceptible to chemical and physical changes in the

water they fall an easy prey to fish of many species and finally they naturally die out when a well dries up

The disease is confined to areas of moderate rainfall Rao has shown that the average rainfall in the endemic areas is between 10 and 40 inches a year It does not occur in the Rajputana and Sind deserts which often have no rainfall during a whole year whereas in the neighbouring Central Indian States where the average annual rainfall may not be more than 12 inches there are many heavily infected areas and the disease never appears in areas of very heavy rainfall such as Bengal and Assam in eastern India In provinces such as Bengal where the rural water-supply is almost exclusively from large *tanks* it is probable that fish, which are constantly present in these large bodies of water play an important part in destroying cyclops and preventing the disease

Further the incidence year by year is dependent on the regular recurrence of suitable seasonal conditions and deviations from these conditions have often been shown to affect the incidence Instances have been recorded where the disease has disappeared for several years after a flooding, which has washed out the cyclops from the wells reduced the organic matter and changed the chemical and physical composition of the water and similarly after a drought which has caused the wells to dry up

On the other hand in villages in which the normal annual rainfall is on the high side 30 to 40 inches a drought that merely reduces but does not dry up the wells will be followed by an increase in the incidence of the disease.

The season when most infections occur is at the end of the hot weather just before the monsoon rains arrive at this time the cyclops are present in the largest numbers as the water is shallow and the organic matter is at its highest concentration Further the concentration of cyclops makes the water particularly infective at this time of year

The incubation period is usually about one year and Rao s collected data show that the curve of the date of onset of symptoms starts to rise in March reaches its peak in July and falls again until October after which it remains at a low level

(c) The presence of cyclops —Conditions may be suitable for cyclops without cyclops being present and the temporary or long standing freedom from the disease of certain village communities has been shown to be due to this fact. After cyclops have been washed out by flooding or dried out by drought it is often several years before the well becomes restocked with cyclops Experiments with animals and even human experiments (Liston Turkhud and Bhave *loc. cit*) suggest that a heavy dose of infected cyclops has to be swallowed to ensure the establishment of infection.

(d) Introduction of infection —Several instances have been reported in which villages in the endemic area have remained free from infection until an infected individual from a neighbouring village arrived and infected the local well Similarly, in an infected village when a well is used by one family or a very limited community the family or the community may remain free from the disease for some time until a member becomes infected by drinking from another well

PATHOLOGY AND SYMPTOMATOLOGY

The third stage larvæ enter the tissues of the definitive host by passing through the mucous membrane and muscular coats of the intestine to reach the loose retroperitoneal tissue where the worms mature and mate. The mature gravid female now migrates in the subcutaneous tissues to a limb where it lies with its head near the extremity of the limb and

the body coiled in the local subcutaneous tissues or extended along the full length of the limb Up to this time the worm has apparently produced no pathological changes in the body of the host this therefore constitutes the incubation period it lasts about one year and during this period there are no indications of infection except perhaps during the last week or so when the worm may possibly be felt by gentle palpation, and patients sometimes state that they have felt the worm moving under the skin. At this point, the worm secretes some apparently toxic substance that usually causes both a general and a local reaction in the subcutaneous tissues

The onset of the general reaction is usually without any warning the patient feels giddy and ill and may collapse, he vomits his pulse is feeble and his heart sounds faint he is cyanosed or very pale, his face may swell and there is usually a painful swelling of the limb that is subsequently the site of the local reaction and he may suffer from an urticarial rash all over the body that is intensely irritating There is usually a slight leucocytosis that is mainly due to an increase in eosinophils This attack which has been described as being allergic in nature but which is not unlike the type of attack that may follow a severe insect sting or even the bite of a mildly poisonous snake usually passes off in a few hours and then the local signs become more prominent. Subsequent attacks, whether in the same season or the following year, tend to be milder this seems to be against the theory that they are allergic in nature and suggests rather that the reaction is due to some toxic substance from the worm to which in time the patient develops some tolerance.

The local reaction follows immediately or is coincident with the general reaction

The site of the local reaction is usually the ankle or the foot, but varies according to the circumstances In India in about 90 per cent of cases the worms point here, as these are the parts of the body which commonly come in contact with water this is probably true of most endemic areas The worm may appear however, in other parts of the body also, e g on the arms, head, neck, chest back abdomen loins groins and scrotum, and very rarely on the tongue and eyelids

Generally, a patient shows only one worm at a time, and when this has discharged its larvæ or has been removed the patient enjoys a little respite until the next year when a fresh worm may appear Cases of multiple infection are however not uncommon. A patient may show two or more worms in the same part or in different parts of the body either simultaneously or as is more common at short intervals. In one individual from Rajputana, as many as twenty two worms were removed at the School of Tropical Medicine Calcutta during one year and as many as fifty-six worms have been found in one person at the same time

There is local red induration and vesiculation and eventually a blister (see plate XXIV) is formed which if the contents are examined, will be shown to consist of a clear yellow serous fluid with neutrophils eosinophils and mononuclear cells but not usually any larvæ. The blister continues to enlarge and at the end of four or five days it may have attained a size of two to two and a half inches in diameter it eventually bursts and then from its tunnel in the subcutaneous tissues the worm protrudes a portion of its uterus that has prolapsed through its mouth or through a rupture in the body wall near the head this loop of uterus bursts and the larvæ swim out (see plate XXIV)

This hole is kept patent by the worm which als protrudes its uterus and discharges larvæ it is an easy poin for septic



Showing blister on the left ankle (foot) produced by guinea-worm



Guinea worm emerging from the ulce
opening of the blister)



Guinea-worm emerging from the leg.



Microphotograph of *Mesocyclops leuckart* in
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This hole is kept patent by the worm which at intervals protrudes its uterus and discharges larvæ it is an easy point of entry for septic



Showing blister on the left ankle (foot produced by guinea worm



Guinea worm emerging from the ulce opening of the blister)



Guinea-worm emerging from the leg.



Microphotograph of *Mesocyclops leuckarti* In with guinea-worm embryos.

[illegible] the [illegible] environment and drawn in [illegible] that secondary infection [illegible] to occur but provided the worm [illegible] the [illegible] mouth of the tunnel in which it lives [illegible] It may amount to an area of redness [illegible] induration [illegible] or tenderness some lymphangitis and [illegible] a little [illegible] of the lymph the glands in the groin. There are [illegible] constitutional symptoms.

The worm may [illegible] before it reaches the surface if this occurs or if the worm is broken while being extracted there will be a sharp local reaction along the [illegible] of the site of the dead worm. This may only amount to cellulitis which eventually subside or there may be subacute abscess formation at different points along the site of the worm or the site may become [illegible] infected and suppurate with the severe local and general reaction. The suppuration may involve important structures tendon sheaths joints or even blood vessels and cause serious complications and even death from pyaemia or septicaemia.

Finally when the inflammation subsides there may be fibrotic changes along the whole site of the worm which may cause [illegible] formation pain and contracture or the remains of the worm may become calcified and cause painful lumps chronic arthritis [illegible] synovitis or neuritis.

The pathological process can thus be summarized —

(i) A period of [illegible] up to [illegible] not associated with any pathological [illegible]
( ) A [illegible] the [illegible] sub-[illegible]
( ) A local reaction [illegible] the subcutaneous tissues at the point of [illegible]
( ) An area of inflammation [illegible] secondary infection, [illegible] of the worm
( ) Cellulitis [illegible] abscess formation [illegible] along the course of the worm if it [illegible] killed
(vi) Fibrosis or calcification with [illegible] complications chronic arthritis, synovitis or [illegible]

IMMUNITY

There is no evidence that there is any natural race class sex or age immunity on the other hand not all those that swallow infected cyclops suffer from the disease

In the human experiment referred to above only one out of five subjects became infected, and very frequently many of the members of a household whose well is heavily infected will escape infection But Powell (1904) reports an incident in which 21 members of a party drank water from an infected well, during a visit of two days only seven of them became infected and showed symptoms from 11½ to 13 months later

There is no evidence that any immunity is acquired as many instances are reported in which patients have been infected year after year in some instances these persons have been subjected to infection for only a short time each year while visiting their native villages Again in a village in Saugor district in India 155 out of a population of 1,095 were infected of these 121 had single and 34 multiple infections The large percentage of multiple infections in this village certainly does not suggest the development of any special immunity after the first infection

It would appear therefore that there is a personal factor that accounts for some individuals being more easily infected than others This factor may not necessarily be of the nature of a true immunity, but it may well be some variable physiological factor such as gastric acidity

* A Poisson series would give only about 15 second infections.

The fact that the general reaction shows a tendency to decrease with successive attacks has been referred to above this suggests development of tolerance to the 'toxin' from the worm.

DIAGNOSIS

This will seldom present any difficulty when once the worm has presented and when one suspects the condition it is often possible to feel the coiled worm under the skin at an earlier date.

The diagnosis can be confirmed by the intradermal test suggested by G W St C Ramsay (1935) the technique of which is as follows —

The antigen —This is obtained from a dried and powdered guinea-worm 0.25 gramme is shaken in 100 c.cm of ether for two hours at room temperature in order to remove the lipoids the residue is rendered ether free and is extracted by shaking in 100 c.cm of 0.85 per cent sodium chloride for four hours at 37°C and after centrifugalization this is passed through a no 6 Seitz filter

Procedure —0.1 c.cm. of this is injected intradermally

Result.—A weal 2 to 3 cm. in diameter with pseudopodia is considered a positive reaction

The exact position of the worm may be ascertained by injecting it with lipiodol and x raying the limb The position of calcified worms can also be demonstrated by skiagraphy

There is usually a marked eosinophilia, up to 15 per cent but this finding is not specific as it occurs in many other helminthic infections.

PREVENTION

The reader should refer back to the paragraphs on Ætiology he will see that the essentials for transmission to occur are, (a) the contamination of the water-supply by an infected definitive host, (b) the presence of cyclops, the intermediate host, in the water supply and (c) the consumption of water containing live infected cyclops by a susceptible person.

Definitive hosts other than man seldom play any important part in the human infection-cycle. The endless chain, man-cyclops-man can be broken at either link or the cyclops can be eliminated

For the disease to be transmitted two elementary principles of sanitation have to be violated and if either is adhered to, that is, if direct human contact with the drinking water-supply is obviated or if the water used for drinking is subjected to even the most rudimentary form of filtration or sterilization the disease will not occur Therefore the most important steps in prevention are education and propaganda, but, in the endemic areas in India at least the habits of the people with regard to washing and drinking are deeply ingrained and amount to a quasi religious ritual against which it is difficult to make headway

The next measure is improvement of the water-supply that is the replacement of the unsatisfactory water-supply by a satisfactory one. Where possible a pipe supply from a protected source should be installed, but the conversion of step-wells into properly protected draw wells, or better still into pump-wells, will be efficacious

There will be many instances when from the nature of the terrain or for economic reasons it is not possible to do this then measures must be directed against the cyclops but any measures of this kind are temporizing measures and this fact should be fully appreciated by those responsible for or interested in, the health of the community concerned.

Measures for the elimination of cyclops may be (i) physical (ii) chemical, or (iii) biological

(i) Physical —The sudden raising of the temperature of water a few degrees will kill cyclops therefore the bubbling of steam through a well has been suggested and used as a means of control Unfortunately the heat

that it is possible to apply by this means does not kill the eggs of the cyclops so that the imagines appear in the well again within a few weeks. It is therefore not a practicable measure.

(ii) **Chemical**.—Most chemicals have the same limitation that is, they do not destroy the egg except in very high unpracticable concentrations. Lime is perhaps the most practicable substance to use as it is often available locally. One drachm of lime in one gallon of water (or about one gramme to a litre) will destroy cyclops. The quantity of water in a well can be calculated from the formula $4.9 \times d^2 \times w$ where d and w are the diameter and depth respectively of the well in feet (or see p. 388).

(iii) **Biological**.—Fish will eat both the larvæ and the guinea worm embryos and Moorthy and Sweet (1936) used this method successfully for controlling guinea worm; the species they recommended were *Barbus puckelli*, *ticto*, *sophore* and *chola* and *Rasbora daniconius*.

To summarize, control is effected by:—

(i) education and propaganda,

(ii) provision of a piped water supply or at least closure of step-wells, or as a temporizing measure by

(iii) destruction of cyclops by physical, chemical or biological means.

TREATMENT

The aim of treatment should be the destruction of the worm, preferably before it begins to give rise to symptoms, but no drug has yet been shown to effect this. In the absence of a specific, the treatment must be aimed at ameliorating the clinical manifestations and preventing the more serious complications of the infection.

It will be convenient to refer back to the six pathological processes summarized above and to discuss the treatment in each case except the first, as in the absence of a specific there is no appropriate treatment at this stage.

(ii) **The general reaction**.—Fairley and Liston (1924) claim that this attack can be cut short by the administration of 10 minims of adrenalin subcutaneously.

(iii) **The local reaction**.—This cannot be prevented, but it can be relieved to some extent by hot and/or cold applications locally.

(iv) **The local inflammation at the point of emergence of worm**.—This can be limited by antiseptic dressings, local hot fomentations and to some extent by the administration of sulphonamides. Early removal of the worm (*vide infra*) will allow this to heal and limit the duration of this stage.

(v) **Cellulitis along the course of the dead worm**.—If it is left, the worm will eventually die and, if its removal is attempted inexpertly, it will break and the remaining portion will die; in either case a nidus for septic infection will be left. Removal of the whole worm is therefore the first consideration under this heading.

Removal of the worm.—The method of removing the worm that has been practised for generations in the villages where the disease occurs is to wind the head of the worm around a small twig or a piece of bamboo and to give the bamboo one turn each day until the whole worm has been removed. The method is frequently successful, but it takes a long time. Manson suggested a modification in which the uterus is first emptied by encouraging oviposition by repeated applications of ice or cold water to the orifice, so that the worm becomes flat and can more easily be removed by the winding process. There is much to be said for this primitive method if it is carried out carefully and with aseptic precautions.

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If the course of the worm can be followed or if its exact position can be shown by injecting collargol, lipiodol or some such substance at the mouth and along the whole length of the worm making it visible under the fluorescent screen, and the course can be marked with a skin pencil, the worm can be removed at one sitting by cutting down on it at intervals, dissecting open the sheath in which it lies and hooking up loops of the worm This can be done painlessly under local anæsthesia

In the event of the worm being broken or of a portion being left, its absorption can be encouraged by hot fomentations applied locally and the administration of sulphonamides to prevent or cure sepsis. Should this fail and abscesses form these will have to be opened in the usual way

(*vi*) **Sequelæ**.—Finally if the worms become calcified or if fibrotic cords are formed that cause pain or interfere with the patient's movements they must be removed surgically

PROGNOSIS

Generally, the patient is only temporarily incapacitated for work during the few weeks following the development of the blister After the complete removal of the worm and the healing of the ulcer the patient may be fit for work until the next season. Sometimes however serious complications develop that may lead even to permanent deformity The patients sometimes develop fixed joints (ankle or knee) as a result of the prolonged immobilization on account of the inflammation and suppuration associated with the disease and become crippled for life

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GNATHOSTOMIASIS

Introduction.—Infection with worms of this genus are apparently not very uncommon in animals but up to 1929 only eleven human infections had been reported Maplestone and Bhaduri (1937) in reporting the fourth case from India expressed the opinion that the infection was probably far more common than had been believed hitherto and quoted the findings of Prommas and Daengsvang (1934) and Castens (1935) in Siam (Thailand) There is thus evidence that the infection is more than a medical curiosity and with a greater awareness on the part of the medical profession a wider distribution of the infection may be recognised.

The infection is not a serious one and the commonest symptom is fugitive swellings in different parts of the body rather than creeping eruptions that are so frequently associated with this infection in textbooks.

Geographical distribution—This appears to be essentially tropical. Cases have been reported from Siam (Thailand) India Malaya China Japan and Queensland More than half the reported cases were observed in Siam.

In Siam more females than males are affected

The parasite.—*Gnathostoma spinigerum* is a relatively short nematode worm varying from 11 mm to 54 mm. in length by about 2 mm. in thickness The immature adult the form that is usually recovered from man may be only about 3 or 4 mm long and about 0.5 mm. in thickness. It has a very distinctive bulbous head around which there are eight rows of hooks arranged ringwise The larvæ measuring less than a millimetre and with only four rings of spines have also been recovered from man The characteristic heads of the adult and larva are shown in figure 161 on p 668

The full cycle has not been worked out satisfactorily but it would appear that the true definitive hosts are large carnivores the tiger leopard dog cat, and weasel have been found infected in nature The ova are ingested by a crustacean (cyclops) in which they develop into larvæ A second intermediate host appears to be necessary fish frogs and snakes have been suggested This second intermediate host is eaten by the definitive host and development is complete (Prommas and Daengsvang, 1936 1937) As however only subcutaneous and submucous infection has been demonstrated in man it is suggested that the larvæ may possibly gain entrance through the skin

Pathology and symptomatology —The usual history is that of a small al swelling of the skin and subcutaneous tissues, somewhat suggestive of angioneurotic œdema which may or may not be painful this disappears completely within a day or so to appear again at a point not far from the original lesion. At other times the swellings appear within a very short time at points a considerable distance from one another This continues often for several months but eventually the worm penetrates to a point just below the epidermis and causes a localized cellular reaction, the site of which becomes secondarily infected, and an abscess occurs, when this bursts it releases the worm, alive or dead. Or it may be seen before any abscess has formed in which case it can be removed without difficulty

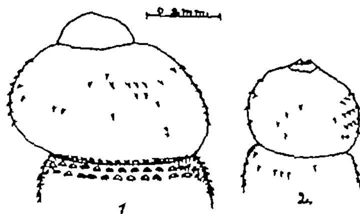


Figure 161 Cephalic extremities of the gnathostome (1) adult, (2) larva.

In a large percentage of cases there has been a history that at some time the worm has migrated in the neck and produced a swelling in the pharynx that caused dyspnœa, and in one case at least the worm has emerged through the mucosa of the pharynx. In others, hæmoptysis, hæmatemesis and/or hæmaturia have occurred, without any other obvious cause, and have not recurred after the worm has emerged or been removed.

Only a very few cases have been encountered in which the worm has burrowed horizontally in the skin and produced a serpiginous itchy raised linear eruption a condition that could be described as ' creeping eruption

Diagnosis.—This can only be made with certainty by removing and identifying the worm but a history of migratory swelling should certainly lead one to suspect this infection, especially if the filarial infections can be excluded

Treatment and prevention —There is no known specific and treatment consists in removing the worm when it shows itself

Until more is known about the ætiology no preventive measures can be recommended

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SCHISTOSOMIASIS

Introduction—There are two main clinical forms of schistosomiasis, namely the vesical and the intestinal *forms*. The causal parasites of both forms are trematodes of the genus *Schistosoma*: the former is caused by *Schistosoma hæmatobium* (Bilharz, 1852), Weinland 1858 and of the latter there are two types which are sufficiently different to warrant separate consideration: one caused by *Schistosoma mansoni* Sambon 1907 and the other by *Schistosoma japonicum* Katsurada 1904. These parasites are usually known as blood flukes.

Historical.—The Ebers *Papyrus* referred to hæmaturia that was probably schistosomal in origin, and confirmatory evidence of the early existence of this infection in Egypt is provided by Egyptian mummies several thousand years old (*20th dynasty*).

Bilharz discovered the flukes in the mesenteric veins at an autopsy in Cairo and later he found the eggs in the urine in cases of hæmaturia. Cobbold was the first to describe the worm, and he gave it the generic name *Bilharzia*, but Weinland's name *Schistosoma* has priority and has come to be accepted, although the word bilharziasis is still used by some writers for the diseases caused by these flukes.

Manson and others suspected that there were two species of schistosome on account of the differences in the clinical picture and the geographical *distribution* of those cases in which the *lateral-spined* eggs occurred. *The name Schistosoma mansoni* was given to the intestinal species by Sambon in *1907*, and the actual difference was finally proved experimentally by *Leiper* (1918) who demonstrated the life cycles of these two parasites. *He* showed that they were *two distinct* species with two different intermediate molluscan hosts and that the route of infection was through the skin.

In Japan, the disease was recognized about a hundred years ago but was attributed to other helminths. Miyagawa (1912–13) and Miyari and Suzuki (1913–14) demonstrated the life cycle of the *Schistosoma japonicum*.

Geographical distribution.—Of the intestinal infections *Schistosoma japonicum* infection occurs in China in the Yangtse valley, along the south-east coast of China as far west as Hong Kong, then *inland as far* north as Canton and in Formosa, the Philippines and the Celebes, and in Japan itself there are five limited foci whereas *S. mansoni* is encountered in North Brazil the Guineas, Venezuela and Puerto Rico and several of the West Indian islands in West Africa along the Congo basin, in Central Equatorial Africa in the northern and eastern part of the Nile delta in Northern Rhodesia, and Tanganyika and Madagascar.

The vesical *infection*—*S. hæmatobium*—is distributed widely through Africa: the endemic area extends along the whole of the north coast, up the Nile valley to Abyssinia and down the east coast taking in the west

coast of Madagascar to Cape Colony throughout which it is endemic It occurs in the tropical countries on the west coast including the Gold Coast, Lake Chad the Cameroons and Nigeria and also at the southern tip of Western Europe in Spain and Portugal and in Palestine Arabia and Iraq

ÆTIOLOGY

The causal organisms —The three species of schistosome have already been mentioned. These schistosomes have five distinct stages during their life cycles namely the ovum (discharged from the definitive host) the miracidium (free-living and in the intermediate host), the sporocyst (in the intermediate host) the cercaria (free-living and in the definitive host) and the male and female adults (in the definitive host)

Man is the only important definitive host of *S mansoni* and *S hæmatobium* but *S japonicum* has many—man horse cattle dog cats rats and mice The intermediate hosts are molluscs of several species and a number of genera

The stages of the parasite that occur in man and his excreta are described below —

Ova.—The mature eggs are a yellowish brown colour with a thin transparent shell through which the mature miracidium can be seen They are oval in shape *S japonicum* is distinctly shorter than the other two but of about the same breadth The range of measurements as given by Craig and Faust (1943) and the distinguishing characteristics of the ova of the three species are shown below —

	Range in microns	*Special characteristics*
S japonicum	70 to 100 by 50 to 65	Small depression near one pole with incurved hook.
S mansoni	114 to 1[illegible]5 by 45 to 68	Prominent lateral spine near one pole
S hæmatobium	112 to 170 by 40 to 70	Distinct spine at one pole

Cercariæ —These are materially the same in the three species though those of *S japonicum* are smaller They consist of an oval or fusiform body and a forked tail The bodies of the cercariæ of *S mansoni* and *S hæmatobium* average about 200 microns their breadth is a little less than half their length the main stem of the tail is a little longer than the body and about 40 microns across, and each prong of the forked tail is about 100 microns long. When they enter their definitive host, they discard their tails and become metacercariæ.

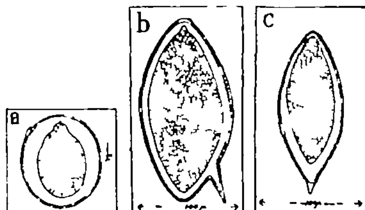


Figure 162 Eggs of (a) *S. japonicum* (b) *S mansoni.* (c) *S hæmatobium*

Adults.—The males are shorter and stouter than the females they measure from 7 to 20 mm. in length and 0.5 to 1.0 mm in breadth and

ve two unequal muscular suckers the smaller one at, and the the ventral aspect near the anterior end. Along its whole len dy of the worm posterior to the suckers is folded ventrally to m naecophoral canal in which the female is held during fertilisati position.

The female is longer and slenderer it has two suckers in relativ ne position, but they are smaller and not so muscular The ich contains 20 to 30 eggs at a time, opens near the anterior end.

The range or average of sizes of the adults of the three spe en below —

	Size in microns	
	Male	*Female*
S japonicum	12 to 20 by 0.50	26 by 0.3
S mansoni	7 to 10 by 1.0	7 to 14 by 0.25
S hæmatobium	10 to 15 by 1.0	20 by 0.25

Life cycle.—In man, the cercariæ are the infective stage. The ough the skin when he bathes or wades in infected water They the skin at the level of the water surface, as the skin dries they ough the epidermis (taking about ten minutes to get beyond the alcohol applied to the skin) eventually they reach a venule a ried in the venous blood to the right side of the heart and the pulmonary artery they reach the lungs They may also enter t buccal nasal or pharyngeal mucous membranes in persons d washing out their mouths with contaminated water, they wou wever survive passage through the stomach In the lungs they ne lung capillaries and cross over to the venous side they are ce more to the heart and thence into the systemic circulation. ese larvæ (metacercariæ) that get into the right traffic lines ar mselves in one of the mesenteric arteries have any future the ching the intestines negotiate a second set of capillaries and, c er to the portal system, reach the liver (The larvæ that fall to mesenteric arteries on the first round probably do not surviv ough to make another complete cycle and negotiate three more illaries, but die and are removed with other blood debris) Wh væ reach the liver they begin to feed and develop they do no r remain here, but turn back into the portal vessels and migrate blood stream

Up to this point the route taken by all three species is the san bsequently their behaviour differs. The larvæ of *S japonicum* y reach the superior mesenteric vein turn into the ileo-colic or th anches here having reached maturity and mated the female, wl d in firm embrace by the male stretches her head end which is d wards the capillaries into the venules of the mucous membrane all intestine and upper part of the large intestine and from her ening, near the head deposits eggs one by one. She then mo other site and repeats the process The miracidia within thes rete a lytic substance which percolates through their shells and al tissue necrosis and eventually ulceration from this ulcerated ar s find their way into the lumen of the gut and are passed out ols

On the other hand, *S mansoni* flukes migrate further into the inferior senteric veins, and oviposit in the venules of the mucosa of the descend- colon sigmoid and rectum the subsequent course of their ova is the ne as those of *S japonicum*

S hæmatobium flukes however go further still and *via* the hæmorrhoidal plexus finally reach the vesical and pelvic plexuses where they oviposit into the venules of the mucosa of the bladder, the ova break through into the bladder and are passed in the urine. The course taken by the majority in each infection has been indicated but there is some overlapping and in *S japonicum* infection there will be many instances in which the adults migrate in the inferior mesenteric vein and deposit their eggs in the mucosa of the descending colon and rectum but they never reach the vesical plexus Conversely *S hæmatobium* ova will sometimes be found in the rectum, but are rarely deposited in radicles of the superior mesenteric vein.

First free-living phase—When the ova, passed in either stools or urine come in contact with water from each a single ciliated larva (or miracidium) hatches. These larvæ, which are approximately the size and shape of the ova are actively motile but are unable to feed and live only about 16 hours

In the snail—They are attracted to certain species of snails (probably by a specific exudate of the latter) whose soft tissues they enter The miracidia enter the lymphatic vessels of the snails there they lose their cilia and develop into sporocysts (first generation) The worms develop for 4 to 8 weeks in the snails mainly in the liver passing through two sporocyst stages finally innumerable (up to a quarter of a million) fork tailed cercariæ burst out of the snail in swarms daily over a considerable period placed at over 60 days by some observers

Second free living phase.—These cercariæ, which are only discharged from the snail in sunlight and do not emerge on cloudy days swim vigorously in the water using their tails as anterior propellers but they cannot feed so that if they fail to find a suitable host within a short time, averaging 24 hours and at most three days they die In this stage they attach themselves to the legs of a bathing or wading human being, or other definitive host discard their tails and by the aid of lytic secretions burrow into his skin to commence a new cycle.

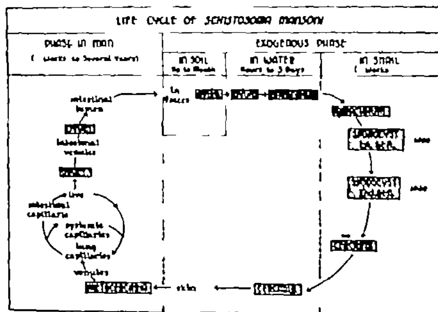


Figure 163

The time factor—This can best be appreciated by dividing the life cycle into different stages. The migrations of all three species up to the time they reach the liver is about five days and the adults of all three species become mature within three weeks from the time of entry of the larvæ In the case of *S japonicum*, approximately another week elapses before the eggs are deposited, in the case of *S. mansoni*, which migrate further, a longer time is required, and in the case of *S hæmatobium*, still longer The total incubation period is therefore shortest in *S japonicum*, and longest in *S. hæmatobium* infection.

Variations in the cycle—While the above is the ideal cycle from the point of view of the worms, the ova, and more rarely the adults will reach a number of other sites. Very frequently ova become detached from the intestinal venules and are carried back into the liver this occurs much more constantly in *S japonicum* infection, in view of the proximity of the superior mesenteric vein. In the latter infection in particular, the ova and even the adult worms may negotiate the liver capillaries or the collateral portal anastomoses and *via* the systemic circulation again reach the lungs or they may be carried to and lodge in other organs and tissues *e g* the brain.

The intermediate hosts.—Craig and Faust (1943) give the following as actual or potential hosts —

For *S hæmatobium* *Bulinus truncatus* (Egypt Cyrenaica and Tunis) *B forskali* (Mauritius, and possibly Kenya Colony), *B tropica* (South Africa), *Physopsis africana* (South Africa and the Belgian Congo) *P globosa* (Sierra Leone West African Coast Northern Nigeria Nyasaland and Rhodesia) *P nasuta* (Kenya Colony) and *Planorbis duforii* (Portugal and Morocco)

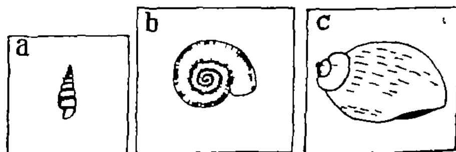


Figure 164 Intermediate host snails

(a) *Katayama nosophora* host of *S japonicum*. (b) Snail of genus *Planorbis* host of *S. mansoni*. (c) Snail of genus *Physopsis* host of *S hæmatobium*

For *S mansoni* *Planorbis boissyi* (Egypt Abyssinia Eritrea Somaliland) *P alexandrinus* and *P herberti* (Sudan), *P pfeifferi* (Natal Southern Rhodesia Sierra Leone) *P sudanicus* (Nyasaland) *P adowensis* (Belgian Congo) *Australorbis glabratus* (Venezuela Lesser Antilles Puerto Rico) *A olivaceus* and *A centimetralis* (Brazil) and *A antiguensis* (Lesser Antilles) and *Physopsis africana* and *Isidora tropica* (Natal)

For *S japonicum* *Katayama nosophora* (Japan and along the coast of China) *K. formosana* (Formosa) *Oncomelania hupensis* (Yangtse basin), *O hydrobiopsis* (Leyte Phillippine Islands)

EPIDEMIOLOGY

The disease occurs mainly amongst populations with a low sanitary standard, or where human fæces in a relatively fresh state are used for

manure In some of these populations the infection is very intense involving as much as 90 per cent of the people as, for example, in some parts of the Nile valley and in Egypt as a whole it has been estimated that six million persons or about half the population are affected either by *S hæmatobium* or *S mansoni* whereas in the heavily populated Yangtse valley tens of millions of Chinese are infected.

The persons most frequently affected in the endemic areas are fishermen rice-field workers washermen and bathers of any kind including ceremonial (Mohammedan) bathers

Amongst foreign sojourners and visitors the infection is often contracted by sportsmen whilst wading through streams or flooded rice fields by sailors whose duty necessitates their wading in contaminated water and by pleasure seekers and children in particular who may wade or bathe in polluted waters.

Instances have been reported *e g* in Egypt and Puerto Rico where sporadic cases have occurred amongst the general population of towns and have been traced to cercaria infected piped water-supplies

Persons of all ages and races are susceptible but there is frequently a male predominance, and children appear to be very susceptible

The season of highest infection in the Nile valley is from February to June when the water in the streams and irrigation canals is low and in Japan during the warmer months of the year May to October but in other places other factors are involved and there is a different seasonal distribution. In the Yangtse valley, for example climatic conditions are favourable throughout most of the year at least from March to November

Factors determining the incidence of the disease —The essentials are —

(*i*) The sources of infection man is the sole reservoir of infection for *S hæmatobium* and probably the only important one for *S mansoni* although monkeys have been found infected in nature but for *S japonicum* there are other important sources for example, cattle especially water buffaloes and in Japan field mice are incriminated but the relative importance of these non human sources does not seem to have been estimated

(*ii*) The presence of snails of certain species to act as intermediate hosts.

(*iii*) Promiscuous defæcation and/or urination a sanitary system by which waterways are polluted, or the use of human excretions for manure

(*iv*) The practice of bathing wading or standing in polluted water or drinking or washing out the mouth with water taken directly (*i e* without storage for at least 3 days) from a polluted source

(*v*) Climatic (especially temperature) conditions that are favourable to the development of the parasite in the snail and to its survival during its free-living stages.

The extent of the incidence of the disease present in any locality will depend on the degree to which these factors are in operation In many places in Egypt and elsewhere the waterways are polluted systematically latrines, for example are built over the streams so that urine and fæces fall into them, or they are used as the main sewer And in China human excreta are stored in large earthenware jars and used as manure in the rice-field If in such areas suitable snails happen to be present the incidence of the disease is certain to be very high indeed. In other areas where pollution is a rare incident the disease will be sporadic and unimportant

Where the specific molluscan hosts have only a limited distribution as in certain places in Japan the disease is localized.

SYMPTOMATOLOGY

Schistosomal dermatitis.—At the time of infection, as the water dries on the skin there may be a tingling sensation which is shortly followed by the development of small urticarial weals at the sites of entry of the cercariæ these disappear rapidly, possibly leaving *macules* Some hours later there may be intense itching, and a localized œdema and papules may appear which may later develop into pustules this condition will usually continue to develop for three days after which it begins to subside.

This condition may develop as a result of infection with any of the three pathogenic schistosomes but it is not constant, and is apparently infrequent in *S japonicum* infection. As noted above, it occurs much more constantly when the cercariæ are those of some schistosome that does not establish itself in man The syndrome is known as swimmers itch in the United States (Cort 1928) and Canada (McLeod 1940) where it commonly occurs amongst bathers in the big lakes.

The febrile attack.—This occurs between the end of the fourth week and the end of the third month. It has been reported as early as the fifth day in *S japonicum* infection but the experience of others and experimental work suggest that these reports of the very early occurrence of the febrile attack should be ignored However, in *S japonicum* infection it occurs usually between the fourth and sixth weeks whereas in *S hæmatobium* infection the average incubation period is about ten weeks in *S mansoni* infection the interval is usually between these two but the febrile attack is not so well defined or constant.

The onset may be gradual or sudden The fever usually rises each evening to about 102 and then falls to normal or the 99 line towards morning There are usually chills and often an actual rigor followed by profuse perspiration during the night. The fever is accompanied by malaise anorexia, pains in the back and along the nerves of the limbs and sometimes by a cough nausea and vomiting, abdominal discomfort and diarrhœa

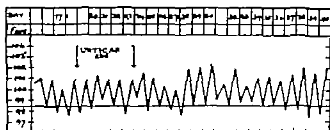


Figure 165

At the same time, or within a day or two an extensive *urticarial rash* appears sometimes with œdema of certain areas There are large weals an inch or two in diameter with a red margin that fades into the surrounding skin. All parts of the skin may be affected and also the mucous membranes of the mouth and throat so that it seems possible that most of the symptoms may be associated with similar local reactions *e g* the cough and the diarrhœa may be due to patches of œdema in the lung—which can sometimes be identified by auscultation—and urticarial swellings of the mucous membrane of the intestine respectively The urticaria as is usual is associated with intense irritation and dermatographia is often observed

The urticaria usually lasts about five days but sometimes longer The fever may last three or four weeks and then fall by slow lysis, or it may fall earlier and after a week or so of remission may relapse, but the second febrile attack is not necessarily associated with recurrence of other symptoms During the febrile attack a considerable loss of weight may be expected

The liver is usually enlarged painful and tender and the spleen palpable.

The period of egg extrusion and tissue proliferation.—At this point the symptomatologies of the three infections diverge and will have to be considered separately.

S. japonicum infection.—The first signs may appear simultaneously with the febrile attack or after a few weeks interval. There will be pain and tenderness in the epigastrium and in the region of the cæcum and then the passage of frequent dysenteric stools in which the ova can easily be found very often with pus and other cellular debris adherent to them. The fever will relapse or continue as a low irregular fever and the patient may pass into a toxic typhoid like state. Anæmia will usually develop. Both liver and spleen will show further enlargement. In the single-incident infection this period will last one to three months and then gradually subside and the organs may recover almost completely, though some dysfunction will be left except in the lightest infections. However in very heavy infections and in the cases of repeated infections that are the rule in highly endemic areas the process will be more or less continuous, with a few quiescent periods during which the symptoms recur immediately when the patient returns to work or otherwise exerts himself and after a few years (3 to 5 years is sometimes the interval mentioned but it must be very variable) the condition will pass imperceptibly into the next stage.

In the final stage, there is increasing emaciation, debility, anæmia, and dyspnœa. Children show stunted growth and intellectual retardation. The dysenteric condition may continue but usually takes on the features of chronic ulcerative colitis there may be some intestinal obstruction with distension of the upper part of the intestinal tract, and alternating constipation and diarrhœa. The liver may enlarge further but usually becomes hard and very fibrotic and tends to contract. The spleen however shows complementary enlargement and may reach the symphysis pubis or the right iliac crest and it also becomes very hard. There are frequently extensive ascites distension of the abdominal veins, and hæmatemesis, results of portal obstruction. The emaciation is profound on account of absorption failure in the upper intestinal tract and liver dysfunction the patient usually develops a sub-icteric tint and sometimes frank jaundice. Jacksonian epilepsy hemiplegia, paraplegia and blindness have followed the deposition of the eggs into the brain the cord or the optic nerve.

Death may occur from inanition from secondary infections such as pneumonia, which may be encouraged by the reaction caused by the ova in the lung *from hæmorrhages or intestinal obstruction or* suddenly as a result of the local reaction to the ova in the heart or brain.

S. mansoni infection.—The course of events is very similar to that in *S. japonicum* infection but on the whole the course is not usually so severe and more symptoms are referable to the rectum. For example prolapse due to the passage of polypoid growths fistulæ fissure *in ano* ischio-rectal and perineal abscesses and hæmorrhoids are not uncommon and occasionally urinary symptoms due to the ova of this fluke reaching the bladder occur. Emaciation is not usually so profound as absorption is not interfered with to the same extent the lesions being mainly in the large bowel.

In Egypt, hepatic and splenic enlargements sometimes occur without any corresponding intestinal lesions (Girges, 1934) and conversely in Puerto Rico intestinal lesions are reported without any liver involvement (Pons 1937).

S. hæmatobium infection.—The urinary symptoms usually do not appear until several months after infection took place and in some cases even several years. The first sign is usually burning and pain at the end of micturition, with the passage of a little blood increased frequency and a

the subject under four headings which correspond to the first four 'essentials

(*a*) **The elimination of the source of *infection*** —In theory the source of infection could be eliminated in the case of *S hæmatobium* and *S. mansoni* infections, by systematic treatment of the population as man is the only important source. This method would be less effective in the case of *S japonicum* infection as there are other definitive hosts. In certain areas, this method has been practised in conjunction with other procedures, with some evidence of success as a means of *reducing* the source of infection but without any real expectation of eliminating it entirely

The educational value of an organised treatment campaign is very considerable, even the most ignorant natives of the endemic areas appreciate the value of treatment and are likely to take more notice of advice regarding prevention given by the doctors who can cure them.

The destruction of rodents and other possible alternative hosts of *S japonicum* should be considered under this heading, but the relative importance of these other hosts has not yet been properly assessed.

(*b*) **Destruction of molluscan intermediate hosts.**—In theory this method promises well in practice except for isolated and limited bodies of water it has been a failure. Periodic drying of irrigation canals reduces the snails, but some burrow in the soil and reappear later The destruction of snails by chemical means *e g 1* in 500 000 copper sulphate will lead to their temporary disappearance but unless the body of water is an isolated one, rapid reinfestation will occur this has been the experience in Egypt.

For small isolated bodies of water when immediate snail elimination is required the introduction of copper sulphate sufficient to make a final solution of 1 in 200 000 to 1 in 500 000 should be applied this can be done by placing the copper sulphate in a bag and towing it behind a small boat backwards and forwards through the water preferably after preliminary removal of aquatic vegetation.

(*c*) **Prevention of contamination of water with human, or other host's, fæces and urine.**—All workers are agreed that this is the pivotal point of prevention but putting it into practice presents difficulties that are usually immediately insuperable.

In the endemic cases in Africa including North Africa and the Nile delta most of the population involved are ignorant peasants with no very high sanitary standards. In the dry parts of the country where there is little rain to wash surface contaminants into the waterways contamination of water must be deliberate and due to inappreciation of the significance of the act it should therefore be easier to prevent under these conditions than in wet countries where fæces and urine deposited promiscuously on dry land will frequently be washed into water

The introduction of proper sanitary systems and education and propaganda are the only solutions but it will be generations before they are fully effective.

Where domestic animals are sources of infection, they should as far as possible be kept away from the vicinity of snail infected water

In China, an *additional* problem has to be faced. There human excreta are stored in *kangs* and later used as manure. If fæces and urine are undiluted with water eggs will survive in these *kangs* which act as septic tanks for only three weeks, so that if several *kangs* are kept and used in rotation and none is used within three weeks of the last addition of fresh fæces the material should be free of eggs and *miracidia*. The addition of an antiseptic such as sodium cyanide, that might add to the manurial value of the contents, has also been suggested as a preventive measure.

(*d*) **Obviation of contact with contaminated water.**—In the case of e foreign visitor to endemic area this should present no difficulties and e knowledge of the existence of the danger should be all that is necessary he sportsman should wear waterproof wading boots in endemic areas In e case of accidental immersions, as the cercariæ do not apparently netrate the skin under water bathing in some antiseptic solution immedi ely on coming out of the infected water should prevent infection. Experi entally it has been shown that cercariæ go beyond the reach of alcohol plied to the skin within about ten minutes so that any delay would llify the effect of the procedure.

In the case of the native his livelihood will often depend on entering ater at frequent intervals, and prevention at this juncture of the trans ission cycle seems to be out of the question. Nursery rice-fields are very potent source of danger as these are heavily manured as far as ssible children, who are particularly susceptible to infection should be ept out of these fields.

Under this heading must be considered the treatment of water that to be used for household purposes. The cercariæ will go through a 30- ich sand filter in five hours so that more efficient filtration chlorination).2 parts in a million Magath 1942) or boiling is necessary if the water to be used in the bath tub or for drinking. The danger here is minimized nsiderably by the fact that free-swimming cercariæ do not usually live r more than a day and it is safe to use water that has been stored in a ail free water storage tank, for say three days, to be on the safe side.

In areas where some domestic animal, *e.g* the water buffalo acts as reservoir of infection every effort should be made to prevent such animals ntering infected water to initiate or renew their infections.

TREATMENT

Treatment must be considered under two headings, specific and sympto- atic.

Historical.—The first successful specific treatment was carried out by Christopherson in 1918, who at the suggestion of McDonogh, used intravenous tartar emetic that had been in use for several years in the treatment of leishmaniasis.

Antimony preparations.—The first drugs to be used were potassium nd sodium antimony tartrate and many believe that even to-day they are he most effective The sodium salt is the less toxic They are given in ? per cent solution in normal saline made with distilled water The solutions must be made freshly or some preservative such as 0.5 per cent phenol, may be added, in which case the solution can be kept at least two weeks It is sterilized by being brought to the boiling point twice prolonged boiling or autoclaving is apt to bring about a change in the molecule It is given strictly intravenously slowly and on alternate days or three times a week. The commencing dose is 2 c cm. or 40 milligrammes the dose should be increased to 3 c cm. 4 c cm. 5 c cm. and 6 c cm., if the patient appears to be able to tolerate it. The principal signs of intolerance are coughing vomiting and joint pains When these occur it may be necessary to increase the doses by only 0 5 c cm. or even to repeat the last dose until tolerance is established A total of at least 2 grammes should be the aim which if all goes well will necessitate 18 injections over a period of 5 or 6 weeks.

Children are given proportionately smaller doses

It appears to be necessary to push the dosage of this drug a little higher than in the case of kala azar (*quod vide* p 168) There is some difference in the tolerance to this drug shown by different nationals

Egyptians appear to tolerate the larger doses well, whereas in Venezuela the intolerance rate is high and it is sometimes necessary to drop the strength of the solution to 1 per cent.

Fouadin (or stibophen) a trivalent aromatic compound of antimony, is less toxic and also can be given intramuscularly It is, in the experience of some workers more effective than the trivalent salts of antimony but, in that of others it has proved less effective Fouadin is marketed as a 6 per cent solution in ampoules The dosage is 1.5 c.cm., 3.5 c cm and 5 0 c cm., on the first three days followed by 5 0 c.cm. on alternate days until a total dose of 45 c.cm. has been given (Khalil and Betache, 1930)

The latest recruit to the antimony preparations is the well advertised but not very extensively tested anthiomaline—lithium antimony thiomalate (Baugé, 1941) Two cubic centimetres of a 6 per cent solution are given on alternate days, the course is 10 injections

Emetine has also been recommended but to be effective it has to be given in dangerous doses, it should therefore be reserved for those cases in which antimony has failed.

Results of specific treatment.—The stage of the disease appears to be more important than the species of the infecting schistosome The treatment will be effective only during the active stages of the infection that is before the third stage of the disease is established and irreparable damage has been done. In the earlier stages of the disease, the improvement is often immediate The action appears to be on all stages of the worm including the ova as the ova that are excreted after treatment has been well established are usually dead later, no more appear, indicating the death of the adult

SYMPTOMATIC TREATMENT

Any attempt to describe the treatment of the very varied pathogenic processes that may result directly or indirectly from schistosome infection would be out of place in this book this treatment will include such varied procedures as the prescribing of 'sulpha drugs for the secondary infections of the bladder in *S hæmatobium* infections paracentesis in the late stages of hepatic involvement in the visceral infections and such surgical procedures as appendectomy splenectomy and removal of polypoid growths.

PROGNOSIS

In the vesical infection the large majority of the attacks are mild and almost symptomless In these and in all early cases the response to specific treatment is good but in advanced chronic cases, when there is much involvement of the bladder wall and pelvic tissues, and when secondary infection has occurred the prospects are poor and the patient will almost certainly die within a short time of sepsis or concurrent disease.

Similarly, in the visceral infections there will be many symptomless infections The course of the disease is on the whole slower and less severe in *S mansoni* than in *S japonicum* infection. In both, response to treatment in the early stages is good but once the liver becomes cirrhotic death within a year or so becomes inevitable. Even in the absence of liver cirrhosis many patients with extensive bowel lesions will die of malnutrition and exhaustion

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OTHER FLUKE INFECTIONS

CLONORCHIASIS

PARAGONIMIASIS

FASCIOLOPSIASIS

CLONORCHIASIS

Historical.—This fluke was first discovered in the bile ducts of a Chinese carpenter who died in the Medical College Hospital in Calcutta in 1874. It was described by McConnell (1875). The life cycle of the parasite was worked out by several Japanese parasitologists, and the most important recent work on the subject was carried out by Faust and Khaw (1927).

EPIDEMIOLOGY

Geographical distribution.—The infection is endemic in China, Korea, Japan, Formosa and French Indo-China. Its brief appearance in Hawaii was probably due to the consumption of fish imported from Japan.

Incidence.—As the infection of man is dependent entirely on the consumption of under- or uncooked fish, the disease will be most prevalent in those groups of the population in which this practice is most common. In Canton, for example, where fish is expensive, the disease is common amongst better-class males who feed in restaurants where specially prepared uncooked fish is served, and it is uncommon amongst poorer class members of the population and amongst women who feed at home, whereas in certain other parts of the country where fish is commonly eaten by the poor, its incidence is wider.

It is uncommon that symptoms due to this infection will occur in children, on account of the time it takes for the lesions to develop.

ÆTIOLOGY

The causal parasite.—Two phases of the parasite are likely to be encountered in man, the adult in the bile passages and the ova in the stools.

The adult of *Clonorchis sinensis* (Cobbold 1875) Looss 1907 is a semi-transparent leaf-shaped fluke, measuring from 10 to 25 millimetres in length by 2 to 3 mm. in breadth, slightly broader and more rounded at its posterior end.

The eggs are ovoid and flask shaped, with a distinct shoulder around the aperture over which the operculum lies. At the opposite pole there is a small knob or hook. The eggs measure 27 to 35 microns by 11.5 to 19.5 micron. They contain a fully-developed miracidium.



Figure 166
The egg of *Clonorchis sinensis*.

Life cycle.—The ova are discharged in the fæces by the definitive mammalian host, and are taken up by the intermediate host, a snail of the appropriate species; here the miracidium hatches out, and the parasite passes through several stages to emerge as a free-swimming cercaria; the cercaria immediately enters under the scales of apparently almost any fish, and encysts in muscles of this second intermediate host, which is then eaten by man or other definitive host; the metacercariæ excyst in the duodenum and migrate up the common bile and hepatic ducts to reach the liver, where they live in the biliary passages and become adults; the eggs that they extrude pass down the biliary passages again to reach the duodenum, and these are eventually excreted in the fæces, when the cycle is complete. The development in man takes about a month, but the whole cycle covers a period of about three months under favourable conditions.

Hosts.—Man is an important definitive host and helps to maintain the cycle, but dogs, cats, badgers, weasels, martens and minks and several other carnivora are also definitive hosts in nature.

Species of several genera of snails act as intermediate hosts, *Parafossarulus*, *Bithynia* and *Melania*, and some 40 species of fish have been found infected.

PATHOLOGY

The pathological reactions to the presence of these flukes appear to result from toxic substances secreted by the adult worms from impaction of clumps of sticky eggs in small bile ducts and possibly from mechanical damage by the adults themselves All the primary changes occur in the liver except in very heavy infections when the pancreas is involved, all other pathological changes are secondary to liver damage

Fibrosis and thickening of the walls of the bile passages throughout *the whole organ with proliferation of bile ducts in certain areas, and both* intra and interlobular cirrhosis are described *Hoeppli (1933) found* extensive changes in 66 post mortem specimens from patients who died from other causes (In view of recent work that has shown that extensive liver changes may result from dietary deficiency it would be well to accept his conclusions as to the responsibility of the parasite in all these cases, with caution)

SYMPTOMATOLOGY

The majority of mild infections are apparently entirely symptomless.

The symptoms are not very characteristic and indicate liver damage generally rather than any specific damage caused by this parasite.

Gastro intestinal disturbances are common diarrhœa and irregularities of appetite a sense of fullness in the liver region and liver enlargement periodic jaundice and later ascites hæmorrhages and other results of cirrhosis are described.

Cardiac and nervous symptoms are also described.

There is usually a leucocytosis and a slight eosinophilia

Diagnosis—The only satisfactory method of diagnosis is by the finding and identification of the eggs in the stools Flotation methods should not be used. Ova may also be recovered by duodenal catheterization

PREVENTION

Personal prophylaxis can be achieved by avoiding the consumption of under or uncooked fish Education and propaganda pointing out the danger of this practice in the endemic areas should be undertaken

As man is an important source of infection, sanitary disposal of fæces will help to reduce the infection in any locality but will not entirely prevent it, as the sanitary habits of other definitive hosts cannot be controlled. Ammonium sulphate added to night soil in adequate amounts will sterilize it without destroying its manurial value.

A third method of control is by the destruction of snails (*vide* SCHISTOSOMIASIS) where this is possible

TREATMENT

There is no entirely satisfactory specific for this infection, but good results have been claimed for gentian violet (*see* p 607) Other drugs used with apparent success are the antimony preparations sodium antimony tartrate and fouadin and the gold preparation solganol B

Prognosis.—This is dependent almost entirely on the weight of the infection It is probable that most light infections are entirely innocuous and do not affect the patient's expectation of life, and the suggestion that even light infections may have serious sequelæ *e g* cirrhosis and carcinoma has never been satisfactorily proven

Heavy infections undoubtedly cause irreparable liver damage and shorten the patient's life. In cirrhosis from whatever cause the prognosis is bad.

PARAGONIMIASIS

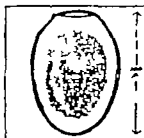
Geographical distribution.—The true endemic areas of human infection are all in Asia, in Japan, Korea Formosa China, Manchuria Indo-China, Siam, and the Philippine Islands isolated cases have been reported from several places in Africa, namely in the Belgian Congo and the Cameroons in New Guinea and in the western hemisphere in Peru Venezuela, and Brazil.

Infection amongst mammals covers a much wider area including India (the first *Paragonimus* identified was found in the lung of a Bengal tiger), Malaya Java and Sumatra It is apparent that sporadic cases may at any time appear in these countries but that the human disease will be truly endemic only where the habit of eating uncooked crustaceans is prevalent

ÆTIOLOGY

The causal parasite.—*Paragonimus westermani* (Kerbert 1878) Braun, 1899 is a relatively thick (3 to 5 millimetres) ovoid fluke measuring 7 to 12 mm. in length by 4 to 6 mm. in breadth slightly broader anteriorly than posteriorly with two suckers one placed at the anterior end and the other in the middle line slightly anterior to the centre of the body of the fluke

The eggs measure from 80 to 120 microns in length by 40 to 60 in breadth they are oval in shape and have a wide opening at one end over which there is a flattened operculum


Figure 167 The egg of *Paragonimus westermani*.

The life cycle.—The egg passed by the definitive host remains in water for several weeks before it is mature the time depends mainly on the temperature. The miracidium emerges and enters a suitable snail after an interval of several weeks during which the parasite passes through several stages it emerges from the snail as a free-swimming cercaria this cercaria actively enters the soft parts of a second intermediate host, a crustacean and in this crustacean it encysts When the crustacean is eaten by the definitive host (e g man) the metacercaria is released from its capsule by the time it reaches the duodenum it penetrates the wall of the duodenum migrates through the diaphragm and pleural cavity to reach the lung.* In a small pocket in the lung which is formed around the parasite, it develops into an adult and when mature extrudes eggs that are coughed up by the host and the cycle is complete If swallowed the eggs remain viable and are passed out with the fæces The phase in the definitive host takes several weeks to complete.

Other organs or tissues in which the metacercariæ may come to rest are the liver spleen brain peritoneum testes prostate epididymis muscles and skin

Hosts.—Besides man the tiger panther leopard wild cat domestic cat, wolf fox, dog mongoose, muskrat and rat can act as definitive hosts.

Melania libertina is said to be the commonest snail intermediate host but *Ampullaria luteostoma* and other species of *Melania* are also potential hosts.

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* It is not clear why metacercariæ should take this direct but somewhat unusual route rather than the more biological one via the lymphatics and systemic blood which would take them straight to the lungs

A number of crustaceans of the genera *Astacus Eriocheir, Potamon,* and others have been found infected, and other crustaceans are probably capable of acting as the second intermediate hosts.

PATHOLOGY

In the lung there is a sharp cellular reaction to the presence of the parasite consisting mainly of polymorphonuclear leucocytes and eosinophils later fibroblasts appear and eventually a thick band of fibrous tissue is laid down around the worm. Within this fibrous capsule besides the worm there is a mass of reddish brown purulent material in which the eggs of the worm can be found Periodically these abscess-like cavities communicate with an adjoining bronchiole and the fluid contents are discharged into a bronchus and coughed up or swallowed by the patient. The worm however remains and the process is repeated. Sometimes several of these cavities or tunnels coalesce, and a comparatively large cavity is formed.

In the other organs and tissues where the larvæ may come to rest and the adult worms develop a similar tissue reaction and abscess formation occurs. In any of these places a secondary infection may take place and the fibrous capsule and its contents be replaced by an ordinary abscess.

SYMPTOMATOLOGY

This will naturally depend on the main site of the encysted worms. When they are in the lung, the condition is not unlike that of pulmonary tuberculosis except that there is not usually any fever There may be an irritating cough which is worse in the morning, and paroxysms may occur when the patient is at rest and disturb his sleep The reddish-brown sputum that the patient coughs up is suggestive of the rusty sputum of pneumonia. There may be a hæmorrhage after a particularly violent fit of coughing In uncomplicated cases physical signs are few but there are usually rales However complications such as broncho-pneumonia pleurisy and empyema are not uncommon.

In the brain, the encysted parasites may cause Jacksonian epilepsy and other cerebral symptoms in the liver they may cause liver pain and enlargement in the intestinal walls they may cause abdominal pain and gastro-intestinal disturbances, in the prostate epididymis and testes, they may cause pain and swelling and in the skin they may discharge at the surface and cause an open ulcer

Diagnosis.—This is dependent almost entirely on the finding and identification of the eggs either in the sputum or in the stools. In the latter case, they may have come from cysts in the intestinal wall that burst into the lumen of the intestine or from the lung having been coughed up and swallowed.

X ray examination has proved disappointing as a diagnostic procedure.

A complement-fixation test has given a high percentage of positive results

PREVENTION

It will be apparent from the ætiology of the disease that there are several points at which the transmission cycle could be attacked but in none of these cases would it be possible to devise any practicable measures

By means of education and propaganda and if necessary legislation the practice of eating uncooked crustaceans should be stopped but even this will not reduce the potential danger as the cycle can probably be maintained satisfactorily through other mammalian hosts so that any future relaxation would probably again lead to the development of fresh cases

TREATMENT

Practically the only treatment for which any success has been claimed is with emetine. Large doses bordering on toxic doses must be given to be of any value. Doses of half a grain three times daily for at least a week have been recommended, and it is claimed that better results are obtained if this is combined with prontosil in full doses

Prognosis.—This is usually fairly good except in the case of very heavy infections or in those cases in which serious complications have already developed

FASCIOLOPSIASIS

Introduction —This is a disease caused by the large intestinal fluke *Fasciolopsis buski* (Lankaster 1857) Odhner 1902 that was first observed by Busk in 1848 in the duodenum of an Indian lascar who died in London. The pig is also a definitive host and probably the main reservoir of infection the life cycle of this fluke includes stages in a snail and in an aquatic plant and the fluke establishes itself in man when he eats the latter

EPIDEMIOLOGY

This infection occurs in India (Bengal and Assam) southern and central China Indo-China and Siam Formosa the Dutch East Indies and Borneo and other East Indian islands. It has not been reported from the other continents

It occurs amongst the poorer members of the native populations of the endemic areas and mainly amongst children who ingest the encysted embryos while they are removing with their teeth the outer covering of the edible portion of certain aquatic plants

ÆTIOLOGY

Fasciolopsis buski is a large broad hermaphroditic fluke from 20 to 75 microns long by 8 to 80 microns across It has one oral sucker at its anterior end The eggs are large 130 to 140 by 80 to 85 microns golden brown in colour and ovoid in shape (plate I figure 16) The shell is thin and has a small operculum (a lid like structure) at one end In the immature egg the contained protoplasm is divided into a large number of regular globular masses which almost fill the shell.

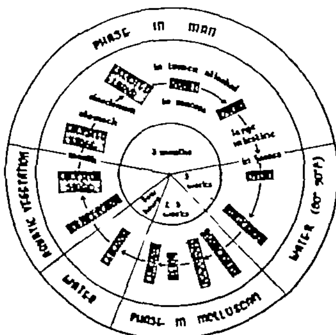


Figure 163 Life cycle of *Fasciolopsis buski*.

Life cycle —Man is infected by consuming raw aquatic vegetation the parasite gaining entry in an encysted larval stage Excystation occurs in the duodenum and the embryo attaches itself to the

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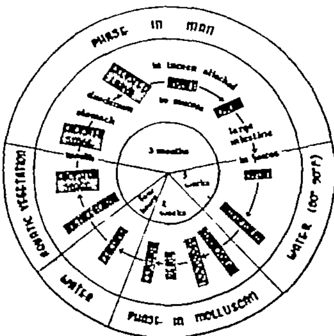


Figure 168 Life cycle of *Fasciolopsis buski*.

Life cycle —Man is infected by consuming raw aquatic vegetation the parasite gaining entry in an encysted larval stage Excystation occurs in the duodenum and the embryo attaches itself to the

HYDATID DISEASE

Introduction.—This is a disease that man shares with sheep cattle and pigs it is caused by infection with the larval or hydatid stage of a small tapeworm, *Echinococcus granulosus* whose definitive host is the dog. Over a period of years these hydatids develop to a very large size in the liver and other organs, producing pathological changes mainly but not

entirely by pressure This disease occurs in temperate and cold climates principally where sheep raising is practised extensively, but it is also encountered in a few tropical and sub-tropical areas

In view of the fact that it is in no sense a tropical disease and that it is usually dealt with adequately in standard textbooks on medicine and surgery hydatid disease is discussed only summarily here

Geographical distribution—Hydatid disease has an extensive distribution throughout the world but the most important foci are Iceland central and south-eastern Europe North and South Africa South Australia Tasmania and New Zealand and Uruguay Argentina and Chile. It also occurs extensively in Palestine, Syria Arabia and Iraq and in Siberia

In India the disease is comparatively rare but perhaps not as rare as published reports would indicate (Editorial 1938) and there are undoubtedly isolated foci where a higher human infection rate exists (Sami 1938)

ÆTIOLOGY

The causal organism—*Echinococcus granulosus* is a minute worm 3 to 6 millimetres in length, consisting of a scolex a neck, and one immature one mature and one gravid proglottid It is an intestinal parasite of the dog the wolf the jackal and rarely the domestic cat The principal intermediate hosts are sheep cattle and pigs but many other animals act as intermediate hosts notably horses and camels. Man is infected sporadically taking the place of an intermediate host in the infection sequence.

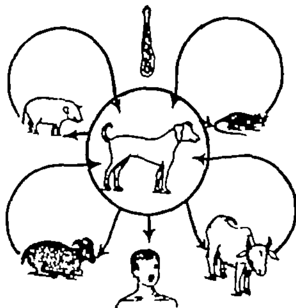


Figure 169

The life cycle—The egg which is indistinguishable from that of the *Tænia* is ingested by the sheep or other intermediate host. In the host's stomach the outer shell is digested off and the onchosphere emerges in the duodenum where it penetrates the intestinal wall to reach the mesenteric venules It is usually filtered out in the liver but may work its way through these capillaries and even those of the lung to reach the systemic circulation and any organ or tissue of the body Wherever it is held up either it is destroyed quickly by the tissue reaction or it develops into a hydatid cyst and commences to grow Within this cyst brood-capsules containing scolices develop When the intermediate host dies or is killed, and is devoured by a potential definitive host these scolices attach themselves to the intestinal mucosa and develop into the adult echinococcus When the adult is mature the terminal proglottid becomes detached and the uterus bursts discharging the ova into the bowel lumen to be passed out with the stools or the detached proglottid itself may pass out of the intestinal canal before discharging the ova. Whichever happens, the cycle is now complete and the ova are ready to be ingested by another intermediate host

(iii) the rupture of an hydatid cyst with the sudden release of large quantities of hydatid fluid containing allergins toxins and daughter cysts into the blood stream, a serous cavity the lung or a hollow viscus (iv) the development of secondary cysts in other organs and tissues and (v) as a common complication, the infection and suppuration of an hydatid cyst.

Distribution of the lesions.—When the onchospheres find their way into the portal circulation the first organ that they reach will be the liver about three-quarters of the hydatid cysts recognized clinically or post mortem occur here of which four out of five are in the right lobe. Some will work their way through the liver and of these roughly half will be held up in the next set of capillaries that is in the lungs about 10 per cent of hydatid cysts are found in the lung. The remainder get through into the arterial blood and are distributed to other organs and tissues the other sites roughly in the order of frequency are skin and subcutaneous tissue bone muscle kidneys spinal cord, brain heart and other organs. The high percentage reported as occurring in the peritoneum are certainly mainly due to metastases from a ruptured primary hydatid.

Development of the hydatid cyst.—Of the onchospheres that come to rest in the various organs, most probably the majority are destroyed by the tissue reactions those that survive develop into hydatid cysts and grow reaching a size of 250 microns in about three weeks They are now surrounded by a characteristic tissue reaction immediately around the cyst are endothelial cells and giant cells which are surrounded by a layer of fibroblasts with new capillary formations and infiltrating eosinophils and an outer layer of denser fibrous tissue When a cyst is located in the liver or other soft tissue it continues to grow and in the sheep by the fifth month has reached about one centimetre in diameter but in man the growth is generally slower and a cyst which may eventually attain the size of a football seldom reaches a sufficient size to be recognizable clinically for about fifteen years unless it is in some vital structure.

As the cyst grows its outer covering becomes thicker and less permeable so that the tissues in which it lies react less specifically but rather as they would to any foreign body The mature cyst consists of three layers one of host and two of parasitic origin namely an outer fibrous-tissue layer a middle laminated hyaline layer which is elastic and usually shrinks away from the outer fibrous coat when the tension within the cyst is relieved and the inner germinal layer The cyst contains albumin free saline fluid under slight tension, in which will be found hydatid sand consisting of brood capsules and scolices Within the original cyst cavity there is often **endogenous budding** with the formation of daughter cysts which separate from the main cyst wall and will develop into individual hydatid cysts should the original cyst rupture into the peritoneum or blood stream for example.

Exogenous budding also occurs In such cases the tumour develops a much more malignant character as it invades rather than compresses the surrounding tissue and eventually a large multiloculated cyst which may involve practically the whole liver will result. Also without rupturing it may give rise to metastases (It is a matter of controversy whether this exogenous budding is not the characteristic of a different species or strain of echinococcus The evidence for this is that it commonly occurs only in a few geographical localities e g in Central Europe but the present consensus is that there is only one species and that some special condition determines its special development.)

When the cyst grows within the skull or the spinal column it naturally produces pressure symptoms at a much earlier date. When it develops in a bone the nature of the tumour is somewhat different as the pressure

causes invagination and the formation of diverticulæ The condition produced is like that of cystic disease of the bone there is rarefaction of the bone and spontaneous fracture is likely to occur

Spontaneous rupture —This is not an uncommon incident Hydatid of the liver usually rupture into the peritoneum or into the gall bladder or bile ducts In the former case the only immediate result may be shock and allergic manifestations but after several years a large number of cysts may develop in various parts of the peritoneal cavity In the latter the daughter cysts may cause a temporary blocking of the common bile duct, but the more serious consequence will be the almost inevitable infection of the cyst cavity

In the lung rupture into a bronchus is not uncommon If the cyst is a large one the incident may "drown" the patient but if he survives this the prognosis is usually good

Suppuration —This may occur in any cyst but in the case of unilocular cyst it is usually the result of a leak or rupture into a hollow viscus The suppuration rate amongst multilocular hydatids is much higher than amongst the unilocular cysts

The changes that occur when hydatid cysts develop in other rarer locations need not be discussed here

Calcification —When a hydatid cyst dies the fluid will be absorbed slowly and be partially replaced by caseous matter The cyst wall shrinks and may become calcified What remains of the cyst is now completely surrounded by fibrous tissue and causing no further symptoms is perhaps discovered *post mortem*

SYMPTOMATOLOGY

Latent period —After infection it will usually be from five to twenty years before the first symptoms appear and it has been estimated that in about 25 per cent of cases the cyst remains symptomless throughout life

Onset and course —The onset of symptoms may be very gradual or it may be sudden either due to the bursting or suppuration of a hydatid cyst. It will be appreciated from consideration of the pathology of the condition that the nature of the symptoms in either case will vary according to the site of the cyst and in the latter according to the direction in which it bursts

When the hydatid is in the liver the first evidence will often be the appearance of a tense cystic tumour possibly exhibiting the characteristic hydatid thrill on percussion in the epigastrium or if the hydatid is near the upper surface of the liver there may be respiratory distress and cardiac embarrassment. It is usually painless. If it bursts into the peritoneum the patient will immediately suffer from shock and possibly an urticarial rash a little later after which there may be another latent period of five to ten years before the secondary hydatids in the peritoneum begin to cause symptoms Or if it bursts into a bile duct there may be biliary colic and obstructive jaundice and later suppuration with pyrexia and other complications associated with a liver abscess If it bursts into the pleural cavity from the liver or from the lung after initial shock the signs will be those of pleurisy with effusion

Multilocular or alveolar hydatids on account of their invasive nature more readily become infected so that irregular pyrexia and pain suggestive of hepatitis or liver abscess will occur without definite rupture

Hydatids in the lung after the usual long latent period may produce slowly increasing dyspnœa or asthma like attacks There may be bulging and deformity of the chest wall but before the cyst has reached such a size there will be an area of dullness absence of breath sounds and opacity

(iii) the rupture of an hydatid cyst with the sudden release of large quantities of hydatid fluid containing allergins toxins and daughter cysts into the blood stream, a serous cavity the lung or a hollow viscus, (iv) the development of secondary cysts in other organs and tissues and (v) as a common complication, the infection and *suppuration of an hydatid cyst*.

Distribution of the lesions.—When the onchospheres find their way into the portal circulation the first organ that they reach will be the liver about three-quarters of the hydatid cysts recognized clinically or post mortem occur here of which four out of five are in the right lobe. Some will work their way through the liver and of these roughly half will be held up in the next set of capillaries that is in the lungs about 10 per cent of hydatid cysts are found in the lung The remainder get through into the arterial blood and are *distributed to other organs* and tissues the other sites roughly in the order of frequency, are skin and subcutaneous tissue bone muscle kidneys spinal cord brain, heart, and other organs The high percentage reported as occurring in the peritoneum are certainly mainly due to metastases from a ruptured primary hydatid

Development of the hydatid cyst.—Of the onchospheres that come to rest in the various organs most probably the majority are destroyed by the tissue reactions those that survive develop into hydatid cysts and grow *reaching a size of 250 microns in about three weeks* They are now surrounded by a characteristic tissue reaction immediately around the cyst are endothelial cells and giant cells which are surrounded by a layer of fibroblasts with new capillary formations and infiltrating eosinophils and an outer layer of denser fibrous tissue When a cyst is located in the liver or other soft tissue it continues to grow and in the sheep by the fifth month has reached about one centimetre in diameter but in man the growth is generally slower and a cyst which may eventually attain the *size of a football seldom reaches a sufficient size to be recognizable* clinically for about fifteen years unless it is in some vital structure

As the cyst grows its outer covering becomes thicker and less permeable so that the tissues in which it lies react less specifically but rather as they would to any foreign body The mature cyst consists of three layers one of host and two of parasitic origin namely an outer fibrous-tissue layer a middle laminated hyaline layer which is elastic and usually shrinks away from the outer fibrous coat when the tension within the cyst is relieved and the inner germinal layer The cyst contains albumin free saline fluid under slight tension in which will be found hydatid sand consisting of brood-capsules and scolices Within the original cyst cavity there is often **endogenous budding** *with the formation* of daughter cysts which separate from the main cyst wall and will develop into individual hydatid cysts should the original cyst rupture into the peritoneum or blood stream for example.

Exogenous budding also occurs In such cases the tumour develops a much more malignant character as it invades rather than compresses the surrounding tissue and eventually a large multiloculated cyst which may involve practically the whole liver will result. Also without rupturing *it may give rise to metastases* (It is a matter of controversy whether this exogenous budding is not the characteristic of a different species or strain of echinococcus The evidence for this is that it commonly occurs only in a few geographical localities *e g in Central Europe* but the present consensus is that there is only one species and that some special condition determines its special development)

When the cyst grows within the skull or the spinal column, it naturally produces pressure symptoms at a much earlier date. When it develops in a bone the nature of the tumour is somewhat different as the pressure

causes invagination and the formation of diverticulæ The condition produced is like that of cystic disease of the bone there is rarefaction of the bone and spontaneous fracture is likely to occur

Spontaneous rupture —This i not an uncommon incident Hydatid of the liver usually rupture into the peritoneum or into the gall bladder or bile ducts In the former case the only immediate result may be shock and allergic manifestations but after several years a large number of cysts may develop in various parts of the peritoneal cavity In the latter the daughter cysts may cause a temporary blocking of the common bile duct but the more serious consequence will be the almost inevitable infection of the cyst cavity

In the lung rupture into a bronchus is not uncommon If the cyst is a large one the incident may drown the patient but if he survives this the prognosis is usually good

Suppuration —This may occur in any cyst but in the case of unilocular cyst it is usually the result of a leak or rupture into a hollow viscus The suppuration rate amongst multilocular hydatids is much higher than amongst the unilocular cysts

The changes that occur when hydatid cysts develop in other rarer locations need not be discussed here.

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under the *fluoroscope* If the cyst bursts into a bronchus, the patient may be asphyxiated by the fluid and the daughter cysts obstructing the bronchi or he may be able to cough up the contents in such cases about 75 per cent recover spontaneously but in others a lung abscess may develop

In the brain the pressure symptoms will usually appear earlier but at first they may amount to little more than headache and visual disturbance and the hydatid may reach a considerable size—demonstrable by *x* ray—before the more serious signs and symptoms of intracranial pressure cause a diagnosis of tumour to be made. Again everything will depend on the localisation Sudden death may occur from pressure on vital areas or rupture of a cyst into one of the ventricles.

In the bones, pain will usually be the first symptom later there may be deformity and spontaneous fracture

In the kidney the condition will be suggestive of a hydronephrosis or a tumour Similarly in other organs and tissues the symptoms will be those of a benign tumour and when it is palpable of a cystic tumour

DIAGNOSIS

This is a matter of very great importance as even in countries such as Australia and New Zealand where the disease is common only about half the cases reported are diagnosed pre-operatively and for proper treatment accurate diagnosis is essential. Diagnosis can be considered under six headings —

(i) Clinical.—The only pathognomonic finding is a hydatid thrill which can usually but by no means always be elicited in the case of large hydatids of the liver Most of the clinical evidence is of a negative nature the slow growth of the unilocular hydatid and its non inflammatory and non invasive nature make possible the development of a very large tumour with the minimum of general or local effects

(ii) Roentgenography —Hydatid cyst on the upper surface of the liver can be recognized by the elevation of the right dome of the diaphragm. Roentgenography is also of great value in locating a cyst in the lung brain or bones When dead cysts become calcified they are well visualized in soft tissues

(iii) Blood picture.—This will provide little help in countries where helminthic infections are common Eosinophilia will depend on there being some seepage of hydatid fluid through the cyst wall and a count of from 10 to 20 per cent will be found in most active cases In the case of a rupture occurring in the cyst wall as a result of ill advised interference or otherwise there will be a sharp rise in the eosinophil count. However a low eosinophil count does not exclude hydatid.

(iv) Serum tests.—Useful information will be obtained from two such tests —

(a) The precipitin test.—This is done with fresh carbolized hydatid fluid, collected aseptically from a sterile hydatid cyst of any intermediate host including man (mixed samples are the best as the fluid from a single cyst may be inactive) or with a 1 in 1,000 dilution of dried hydatid material To a tube containing a small quantity of fresh or reconstituted hydatid fluid an equal quantity of the patient's serum is added after 36 hours, a fine flocculent precipitate will appear in 60 to 80 per cent of cases of hydatid disease

(b) The complement fixation test.—This is done with fresh or dried hydatid fluid or with an alcoholic extract of scolices as the antigen A higher percentage of positive results will be obtained with this test this is usually placed at 80 per cent, but some workers claim that it is always positive in all *active* cases, that is in all those cases in which the cyst is not completely shut off The test remains positive up to a year after the removal of a hydatid cyst.

(*v*) **Intradermal (Casoni) test.**—This is probably the most useful of the immunological tests, it gives the highest percentage of positive results and if the test is carefully done, these will include very few false positives It can be done with fresh hydatid fluid (of proved activity) with a saline dissolved alcoholic extract of scolices or with a standardized heterologous tapeworm antigen. This latter can be made from almost any tapeworm It is best to use a 1 in 100 dilution and to give 0 01 c cm. by intradermal injection There is an immediate weal of at least one centimetre in diameter with pseudopodia

(*vi*) **Identification of hydatid material.**—It is not good practice to tap a cyst through the abdominal wall as, even if the procedure is followed immediately by open operation some fluid with contained daughter cysts may escape into the peritoneal cavity and give rise to metastases However other opportunities for examining hydatid fluid with its contained brood-capsules and scolices will arise, as for example when a cyst bursts into a bronchus and the contents are coughed up in such a case the brood capsules may be mistaken for grape skins

PREVENTION

The reader should again turn to p 698 where the factors in the infection of man are discussed

The dog is not only the most important definitive host, but he is the link between man and any other reservoirs of infection Measures must, therefore, be directed towards—

(*a*) The prevention of infection in dogs by proper control of town and country abattoirs so that dogs do not have access to the entrails of infected animals

(*b*) The destruction of stray and superfluous dogs the proper control of dogs and of other possible definitive hosts and the prevention of their access to places where they could infect food or water designed for human consumption or to the pastures of sheep cattle or pigs.

(*c*) The reducing of the direct association between dogs and man this can be done by reducing the number of dogs as above but also by

(*i*) keeping dogs out of the houses

(*ii*) not allowing them to lick out plates or other utensils used by man

(*iii*) avoiding the fondling of dogs and

(*iv*) forbidding children from playing with dogs

These measures against dogs are particularly applicable in countries where there is a high percentage of infection amongst dogs In other countries the precautions might be relaxed regarding individual dogs that are known by careful and repeated examination of their stools to be uninfected and that are kept under proper control so that their chances of access to infected material are minimal.

Some of these measures can be aided by suitable legislation, but education and propaganda will be essential to achieve success in the prevention of this infection Already a very considerable degree of success has been achieved in Australia and New Zealand, and also in Iceland

TREATMENT

No drug has yet been found that has any specific effect on the parasite in the stages in which it occurs in man It seems very possible that a specific might be found that would destroy the parasite in its early stages, but it would be difficult to establish its efficacy and its practical use would be limited to the periodic administration to those under serious risk however even in such cases other preventive measures would be preferable

The insulation of the cyst by the thick fibrous capsule that occurs in its later stages makes it problematical if a drug will ever be found that will penetrate the cyst and destroy its contents Treatment must therefore be expectant or surgical

Surgical.—Whether this is possible or not will naturally depend on the location of the hydatid. Hydatids of the liver are those that call for surgical treatment most frequently The aim must be to remove the contents and the parasitic layers of the cyst and to close the cavity as far as possible without open drainage This must be done without any contamination of the peritoneal cavity with the hydatid fluid.

It would be out of place to describe the surgical procedures in detail here, but the most recent methods include opening the abdominal cavity to display the cyst selecting a suitable point for aspiration surrounding it with swabs to take up any possible leaking fluid, aspirating most of the cyst contents injecting up to 50 c cm of 10 per cent formalin to destroy the daughter cysts and scolices cutting down on and shelling out the parasitic layers of the cyst and again swabbing out the cavity with 10 per cent formalin

Prognosis.—Hydatid disease is always a serious condition but its seriousness depends very largely on the location of the cyst, and, when operative treatment is undertaken on the experience and skill of the surgeon. In the hands of a skilled surgeon the immediate prognosis in unilocular liver hydatids is good, but recurrences in the peritoneum still occur in a considerable percentage of cases The prognosis in multilocular and suppurating hydatids is bad

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NUTRITION AND NUTRITIONAL DISORDERS IN THE TROPICS

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NUTRITION AND NUTRITIONAL DISORDERS IN THE TROPICS

NORMAL DIETETIC REQUIREMENTS

Introduction —For growth and repair of the human frame and for the production of energy a certain quantity of food is necessary The three energy producing principles of food are protein fat and carbohydrate, but there are a number of other essential nutrient elements for example, mineral salts the most important of which are those of iron calcium, and phosphorus and the vitamins water is also essential The food requirements of man have been studied very extensively although it would be absurd to suggest that there was not a very great deal more to be learned. The energy value of different food substances and the energy requirements of the organism can be estimated (The unit of expression is the large calorie that is the amount of heat required to raise one gramme of water one degree centigrade) The energy value of one gramme of protein is four calories carbohydrate has the same calorie value as it is usually called and a gramme of fat will produce nine calories of energy (or heat) Although the calorie value of the mineral salts and vitamins is negligible they are essential for body building purposes and for the proper utilisation of the energy producing foods

Calorie requirements.—The calorie requirements of man vary according to the age and size of the individual as well as the type of work that he or she is doing. There are formulæ for calculating calorie requirements dependent on weight and body surface but for practical purposes it is usual to take a basic calorie allowance to apply coefficients for individuals of different ages and for special conditions such as pregnancy and lactation and to add supplements for special types of work. The calorie requirement of a man living in a temperate climate and not engaged in manual work is usually considered to be 2,400 calories, the coefficients and supplements to be applied are given in the table below —

TABLE A*

Work	*Supplementary allowance*
Light work	75 calories per hour of work
Moderate work	75 to 150 calories
Hard work	150 to 300 calories
Very hard work	300 calories upwards

Age in years	*Coefficient*	*Calories*
1–2	0.35	840
2–3	0 42	1,000
3–5	0.5	1,200
5–7	0.6	1 440
7–9	0.7	1,680
9–11	0 8	1,920
11–12	0 9	2 160
12–15†	1.0	2,400
Males 15 upwards	1 0	2,400
Women, not pregnant	0 9	2,160
pregnant	1.0	2 400
lactating	1.25	3,000

* League of Nations (1936)
† Meets needs of puberty

It is not uncommon to apply the coefficient of 0.9 as a maximum to women except of course pregnant and lactating women. For babies under the age of one year the caloric requirements are best supplied on a body weight basis thus —

Under six months	100 calories per kilogramme, or 45 calories per pound
Six months, but under one year	90 calories per kilogramme or 41 calories per pound

An allowance will also have to be made for the muscular activities of children: this is usually calculated as 75 calories per hour of active play for boys between 5 and 11 years of age and girls above 5 years and from 75 to 150 per hour for boys above the age of 11 years, that is to say the same allowance as for light and moderate work respectively. Although it is important that the full calorie requirements should be supplied, the exact proportion of the various constituents is not a matter of vital importance, but in a well balanced diet in temperate climates the proportions should be roughly

protein : fat : carbohydrate = 1 : 1 : 5

It is however essential for purposes of body building that a diet should include a sufficiency of good protein.

The composition of all common foodstuffs in terms of protein, fat and carbohydrate has been worked out and can be read from the many tables that have been prepared; these tables usually give the calorie value of a given weight of the substances, but if they do not this can easily be calculated from their composition.

Protein requirements.—The protein intake of an adult should not be less than one gramme per kilogramme (or 0.45 gramme per pound), but the requirements of growing children are proportionately very much greater; the amounts shown in the following table are recommended —

TABLE B

Age in years	Protein requirements grammes per kilo of body-weight
1–3	3.5
3–5	3.0
5–12	2.5
12–15	2.5*
15–17	2.0
17–21	1.5
21 upwards	1.0
Women pregnant 0–3 months	1.0
" 4–9	1.5
lactating	2.0

* Meets needs of puberty.

Protein is built up from chemically simpler substances, amino-acids. During metabolism these are absorbed and rearranged as body protein. There are about 22 different amino-acids, some ten of which, including tryptophane and lysine, are essential, whereas the remainder appear not to be; there are thus good proteins and poor proteins. While there are many good proteins derived from vegetable sources, as a general rule the proteins from animal sources are the better and some animal

protein should always be included in a diet especially the diets of growing children and pregnant or lactating women

Fat requirements —There is no generally accepted minimum standard for this dietary element and the optimum intake will undoubtedly vary considerably with the climate in a temperate climate while 100 grammes is often given as the optimum most dietitians place the minimum at 50 and 60 grammes Perhaps more important is the nature of the fat and at least half should be of animal origin A function of fat is its vitamin carrying capacity, and fats of animal origin are on the whole a richer source of vitamins, however perhaps more important, fat dissolves and increases the absorption of the fat-soluble vitamins. Further certain unsaturated fatty acids *e g* linoleic and arachidonic acid appear to be essential dietary elements

Carbohydrates —These are the main sources of energy and except under starvation conditions are more likely to be taken in excessive than in deficient quantities They are the main constituents of cereals and root vegetables and sugar consists solely of carbohydrates.

Mineral requirements.—Very small quantities of these are required, but the minimum requirements have been calculated.

Calcium —Fish milk eggs and vegetables are rich in calcium. Cereals, especially rice are poor sources whole meal is however a moderately good source

The daily requirement of an adult is about 0.7 gramme but that of a child who needs an excess of calcium for bone formation, is at least 1 0 gramme of a pregnant woman 1.5 grammes and of a lactating woman 2 0 grammes

Phosphorus —This is seldom deficient in any diet adequate in calories and other essentials It occurs in most food substances and cereals are a rich source of phosphorus, some will be lost in washing and cooking.

Iron.—This occurs in many foods in cereals pulses (legumes) fruits vegetables, and meat, especially liver but it is present in negligible quantity in milk. Iron is not however assimilated from the food quantitatively in some foods most of the iron is available that is to say, easily assimilated, whereas in others little of the iron present is available The older tests for availability of iron have been discredited and the only reliable test is the biological one which has not yet been applied to many foodstuffs therefore the iron figures in diet tables have to be interpreted with caution. However with the exception of milk diets, almost any diet that is adequate in calories will contain sufficient iron for normal conditions It is in abnormal conditions such as pregnancy and excessive menstrual loss and in diseases in which there is a continuous loss of blood *e.g* hookworm infection and hæmorrhoids that there may be a *relative* iron deficiency even in persons on a good diet. The infant is born with about three months iron supply stored in its liver so that only when a pure milk diet is extended beyond this period it is necessary to give additional iron but the pregnant woman has to find this additional iron so that her requirements are greater and she is very liable to suffer a relative deficiency

The daily iron requirements of the adult have been placed at 12 milligrammes, but in criticising a diet one should expect at least 20 milligrammes to allow for some of the iron not being available A far better indication of iron deficiency in a population will be obtained by blood examination of a sample of the population than by a diet survey A hypochromic anæmia in a large percentage of a population in which there is no widespread infection with ankylostomes or schistosomes will almost always be due to a deficient iron intake and such an anæmia even in the presence of one

TABLE C

Vitamin		Names	Solubility	Sources	Stability	Physiological action	Average adult daily requirements: International units	Average adult daily requirements: Milligrammes	Pathological effect of deficiency
A		Anti-infective Carotene = provitamin	Fat soluble	Green vegetables, carrots, butter liver some fruit eggs, and red-palm oil.	Prolonged heating destroys	Essential for cell growth and replacement, especially affects epithelial tissues. Precursor of visual purple	5,000	3 00	Bitot's spots, xerosis, and xerophthalmia keratomalacia night-blindness phrynoderma or follicular hyperkeratosis dentine defects.
B complex	B_1	Thiamin Aneurin	Water soluble	Yeast unmilled cereals, nuts and vegetables, some fruits, glandular organs, meat. (Milk is a poor source and milled cereals very poor)	Heat-labile withstands 120 C cul solubl	Controls carbohydrate metabolism by carboxylation of pyruvic acid	330 to 660	1 to 2	Beri-beri polyneuritis anorexia, cardiac dilatation
	B_2	Riboflavin. Yellow enzyme	Water soluble	Pulses, milk products, liver eggs, meat some green vegetables and tubers, yeast. Autolysed yeast (marmite)	Heat stable Light sensitive	Factor in enzyme system that regulates cell oxygenation and affects protein and carbohydrate metabolism.		2 to 3	Ariboflavinosis or cheilosis, glossitis and eye affections dermatitis
	om plex.	Nicotinic acid Niacin.	Water soluble	Meat, liver yeast, whole cereals, potatoes, carrots, pulses. (Milk is poor eggs negligible source)	Heat stable	Same as riboflavin and may also affect water and iron metabolism.		20	Pellagra, or dermatitis, glossitis, gastro-intestinal and mental disturbances.

requirements of vitamin C), (c) endocrine deficiencies (*vide infra* myxœdema and pellagra), and (d) the personal factor (an expression that is a cloak for our ignorance) Again, vitamin deficiencies are seldom single for, if a diet is deficient in one vitamin, it will usually be deficient in one or more other vitamins especially in those found in the same foodstuff Examples of grouped deficiencies are the fat soluble vitamins A and D, and the water soluble B vitamins.

Our summed knowledge of the vitamins has already reached vast proportions and is increasing daily There are many vitamins, their number is continually being added to and the named vitamins are frequently being divided and subdivided Not only do we know in what foods they are to be found in large and small amounts, and what diseases and minor disabilities their deficiency causes but in many instances we know their chemical formulæ and the exact daily minimum requirements of the human organism The writer does not propose to discuss the various vitamins in any detail here but only the special dietetic problems that are likely to face the worker in the tropics The reader who is not familiar with this important subject is advised to refer to one of the many standard textbooks on dietetics but in order to help him to follow the subsequent discussion on the dietary deficiencies encountered in the tropics, a table giving summarized data on the important vitamins is appended (*see* table C)

DIETETIC REQUIREMENTS IN THE TROPICS

The basic dietary requirements in the tropics are naturally very much *the same as they are in temperate climates at least qualitatively* but it has been *found* that quantitatively certain reduction should be made. Aykroyd (1941) considers that the caloric requirements of the average male adult Indian, *for example, engaged in a sedentary occupation* is 2,160 calories or 10 per cent less than that of the average native of temperate western countries *to this* he adds 450 calories for the light to moderate work in which the average agriculturist is engaged making a total 2 600 in round figures To this figure he applies the following coefficients —

TABLE D

	Coefficient	*Calories required (to nearest 100)*
Adult male (over 14)	1.0	2,600
female (over 14)	0.8	2,100
Child 12 and 13 years	0 8	2 100
10 11	0 7	1,800
8 9	0.6	1 600
6	0.5	1,300
4 5	0 4	1,000

For pregnant women he allows 2 400 calories and for lactating women 3 000 For those *engaged in heavy manual work a further allowance must* be made *on the lines of the allowances made for hard work in temperate* countries (*quod vide*)

Protein —*Vegetable proteins are as a rule poorer* than animal proteins (*vide supra*) and, as a large *percentage of the natives of the tropics* are vegetarians or virtually vegetarians either on religious or economic grounds it is difficult *to include* sufficient good protein in their diets. As a minimum at least *one*-fifth of the protein should be of animal origin and for growing

children and pregnant and lactating women the proportion should be higher It will be seen from the table of biological values of protein that even if meat is taboo milk and eggs can be taken to provide protein of high biological value

Fat.—The fat requirements are certainly less than in temperate climates A diet containing 50 grammes of fat need scarcely be considered deficient in fat, and one containing the classical 100 grammes will usually be too rich for either the native or the sojourner in the tropics Again however it is important that some of the fat should be of animal origin partly because some animal fats are richer in vitamins Most vegetable fats are very poor in vitamin A An exception to this rule is red palm (*Elaeis guineensis*) oil which is rich in vitamin A, this palm grows in Malaya Burma and West Africa whence some is exported to other tropical countries but little of this oil is consumed in India or China Other vegetarian food that are rich in vitamin A are nuts and soya beans

Mineral salts and vitamins —There is no satisfactory evidence except possibly in the cases of vitamin B_1 and choline that the requirements of these are in any way different from those in temperate countries However the blood depredations of parasitic infections more common in the tropics than elsewhere make the average iron requirements greater than in the temperate zones and conversely the oral vitamin D requirements are usually less on account of the longer periods of sunlight to which people are subjected in the tropics (see p 6) Iron cooking vessels are often used in the tropics and this probably helps to meet the demand for iron.

Some tropical dietaries.—Data from several tropical countries are available but India with its four hundred million inhabitants and its varied climatic conditions and racial types provides a sufficiently wide variety of diets to form the basis of a discussion on tropical dietaries India has possessed an efficient nutritional research unit for about 20 years This was started by Sir Robert McCarrison under the auspices of the Indian Research Fund Association and for the last eight years has been ably directed by Dr W R Aykroyd who in his nutrition laboratories at Coonoor and elsewhere has carried out a systematic investigation of Indian dietaries as well as much research work arising therefrom and has in many aspects of nutritional investigation given a lead to other tropical countries The following table and comment on Indian dietaries is taken from a paper by Dr Aykroyd (1941*a*)

> It has been found that the diet of the poor rice-eater is much the same all *over India In addition to his staple cereal he consumes only very small quantities* of pulses, vegetables and meat Intake of pulses is usually from 0.5 to 1.5 ounces daily non-leafy vegetables 2 to 6 ounces vegetable oil less than 1 ounce Consumption of meat fish and eggs rarely exceeds 1 ounce and as a rule not even this amount is eaten Leafy vegetables are taken in small quantities while the consumption of milk is usually negligible Fruit is a rare ingredient in the diet. Much the same is true of diets based on millet Wheat diets usually include more milk since, generally speaking milk production is higher in the wheat eating parts of India than elsewhere Middle-class diets differ from those of the poorer classes chiefly in containing a smaller proportion of cereal and more vegetables fruit and, in the case of non-vegetarians more milk products and meat In many areas two or more cereals may be included in the diet other ingredient being limited as described above
>
> In about 30 per cent of the surveys which were carried out in widely separated areas the average calorie intake was below 2,300 per consumption unit, i.e. below any reasonable standard of requirements Again, within certain groups som 30 to 40 per cent of families were not obtaining enough food While it is not justifiable to apply these results to India as a whole there can be no doubt that a high percentage of the population is habitually underfed and the extent of under nutrition is of fundamental importance Enough food takes precedence over the right kind of food and to produce more food must be the foremost aim of agricultural policy

To summarise, it can be said that 30 to 50 per cent of the indigenous inhabitants of India do not eat enough food and that the diets of the great majority are deficient in several important elements. The diet of the rice-eater is usually deficient in iron and under conditions of unusual heat chlorides will also be relatively deficient. Many diets are deficient in fat-soluble vitamin A and in vitamin B_2 complex unless the people take some form of 'country' * beer. Vitamin B_1 is deficient usually only in the diets of those who use raw milled rice. Vitamin C is commonly deficient. Deficiency of vitamin D is not common but in some localities e.g. the south side of deep valleys where the hours of direct sunlight are few and under special social conditions e.g. where women live in *purdah* and children are protected over zealously there may be some vitamin D deficiency.

These remarks can probably be applied to the native inhabitants of most other tropical countries and certainly to those whose staple diet is rice maize or some poorer food substance such as tapioca.

Rice.—As rice is the staple food of about half the inhabitants of the globe, it is entitled to a few lines of special discussion. There are of course some scores if not hundreds of varieties of rice plant, but it will not be possible to discuss this aspect of the subject here. The gross nature of grain of all varieties is the same and their chemical composition is so similar that it is possible to adopt average figures that can be applied for practical purposes to all varieties.

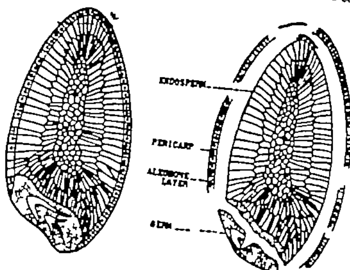


Figure 171

When threshed from the ear the grain consists of an outer inedible husk and an inner edible grain. The latter consists of an endosperm, with its thin outer layer of aleurone cells, the surrounding pericarp and the germ. The bulk of the endosperm consists of carbohydrate, the aleurone layer contains most of the protein and fat and the vitamin B is mainly in the germ.

There are several ways of preparing the grain for eating and the composition of the final product depends largely on the way it is prepared. The primitive method, a method that is still followed by the large majority of peasants who grow their own rice, is pounding the grain with a heavy wooden pestle in a large wooden or stone mortar. This removes the husk, some of the pericarp and usually most of the germ. The more sophisticated method is by machine milling in a rice mill; by this method not only the husk, the pericarp and germ but also the greater part of the aleurone layer of the endosperm are removed, and there is

* Country beers are crude alcoholic beverages made by fermenting various grains; unlike ordinary beer they are sometimes rich in vitamin-B complex.

considerable loss of protein fat iron and vitamin B_1. There are different degrees of milling and the extreme degree of milling is carried out by rubbing the rice between two leather surfaces this removes the last traces of the aleurone layer and pericarp, and leaves a polished pearly white grain. Rice thus treated is known as *polished* rice whereas after ordinary milling it is known as *milled* rice. In either case the part removed is known as rice polishings these polishings are naturally rich in protein fat iron and vitamin B

A procedure that has mainly been practised in India and is now spreading to other countries is known as parboiling (part boiling) The rice still in the husk is first soaked in water, then steamed for some time dried and finally husked by one of the methods mentioned above Parboiling has the practical advantage that it makes newly harvested rice more digestible and facilitates husking but its real value from the nutrition point of view is that both the iron and vitamin B_1 and to some extent other B vitamins also in the germ are dissolved and much of these is absorbed by the endosperm therefore much less of the iron and vitamin are lost during subsequent husking

The following table shows the effects of milling and parboiling on the composition of rice —

TABLE G

	RAW RICE		PARBOILED RICE	
	Milled	*Home pounded*	*Milled*	*Home pounded*
Protein, per cent	6.9	8.5	6.4	8.5
Fat,	0.4	0.6	0.4	0.6
Calcium	0.01	0.01	0.01	0.01
Phosphorus	0.11	0.1	0.15	2.28
Iron mg	1.00	2.80	2.20	2.80
B_1 I U per 100 g	20	60	70	90
Digestibility	+++	+	+++	++
Storing properties	Good	Poor	Poor	Very poor

There is further considerable loss up to 50 per cent of important ingredients during washing and cooking especially if the cooking water is discarded which of course it should not be If for cooking the right amount of water is used all the water is taken up by the rice by the time it is cooked

It will thus be obvious that the practice of machine milling is a bad one from a nutritional point of view One might ask Why then is it practised and why is it difficult to eradicate the practice ? There are several reasons for this some of which are sound others are not Firstly (*a*) the industrial worker finds it very convenient to buy rice ready for cooking instead of pounding it himself This saving of trouble will often appeal to the villager also and he frequently takes his rice to be milled this is done almost free of cost because the miller makes his profit out of the polishings (*b*) When rice has to be conveyed some distance freight is saved if the husk is first discarded In this mechanical age, it would be economically impossible to hand pound rice in large quantities and further (*c*) milled rice keeps much better than home-pounded rice (*d*) Unhusked rice keeps well if it is stored in a dry and well ventilated place as the husk protects it but, when the husk is removed the fat in the aleurone layer is exposed to attack by micro-organisms and becomes rancid

very quickly Parboiled rice even if subsequently milled does not keep as well as raw milled rice Finally (e) æsthetically a plate of spotless white rice is much more appealing than one of flecked and discoloured home-pounded rice Thus, it will be seen that the problem is not altogether a simple one, but the dangers to health in allowing persons who eat little else but rice to use polished rice are so great that it is essential that these difficulties should somehow be overcome.

One method is to limit the degree of milling to which rice may be subjected. Another would be to improve the mechanical methods of husking rice Experiments have been carried out with a wooden grinder and it has been shown that by using this three times as much fat and vitamin B_1 are preserved as when the same sample is subjected to machine milling

The introduction of legislative measures to prohibit machine milling is likely to be resisted on account of vested interests Further in a locality where the milling has been practised for many years and the people have acquired the habit of buying milled rice in small quantities as they require it it would be impracticable suddenly to prohibit the milling of rice.

THE EFFECTS OF DEFICIENT DIET ON HEALTH

General effects

It may be taken as axiomatic that the physique of a nation is dependent to a large extent on its food Numerous examples of peoples of the same racial type living under comparable climatic conditions in which those taking a better diet are physically far superior could be quoted e g in Africa the men of the Masai tribe, whose diet is largely milk and meat are on an average five inches taller than those of the Kikuyu tribe who live on a poor vegetarian diet and the northern Indians who live on a good diet with wheat as the staple cereal and plenty of milk are physically much finer types than the rice-eating southern Indians It is however harder to appraise the effect of diet on health, as distinct from physique that is on morbidity and mortality, as so many other factors come into operation. In India, at least a third of the population is quantitatively underfed and an even greater proportion lives on a qualitatively defective diet (vide supra) and the health of the country is admittedly very bad the expectation of life at birth was calculated to be 26 to 27 years in 1931 compared with 58 9 for England and Wales (1933), 61 9 for Sweden (1926–30) and 68 for New Zealand (1933) The two facts can undoubtedly be connected, but how much of this ill health can be attributed to malnutrition and how much to other factors? The modern sanitarian believes that nutrition is a matter of primary importance. Sir Alexander Russell then public health commissioner with the Government of India in his report for 1935 wrote —

> No preventive campaign against malaria against tuberculosis or against leprosy no maternity relief or child welfare activities are likely to achieve any great success unless those responsible recognize the vital importance of this factor of defective nutrition and from the very start give it their most serious attention Abundant supplies of quinine and multiplication of tuberculosis hospitals sanatoria, leprosy colonies and maternity and child welfare centres are no doubt desirable if not essential but none of these go to the root of the matter The first essentials for the prevention of disease are a higher standard of health, a better physique and a greater power of resistance to infection These can only be attained if the food of the people is such as will give all the physiological and nutritional requirements of human frame

But it is not easy to provide proof from public health returns

Similarly the clinician cannot fail to believe the importance of diet when he sees the various major and minor defects melting away as his

TABLE II

Name of foodstuff	Protein %	Fat %	Carbohydrate %	Calcium (Ca) %	Phosphorus (P) %	Iron (Fe) mg %	Vitamin A I.U. per 100 g	Vitamin B_1 I.U. per 100 g	Vitamin C mg per 100 g	Calories per 100 grammes	Calories per ounce	Biological value protein
Rice raw home-pounded	8.5	0.6	73.0	0.01	0.17	2.8	4	60		351	100	
Rice parboiled, home-pounded	8.5	0.6	77.4	0.01	0.28	2.8	15	90		319	99	80
Rice raw, milled	6.9	0.4	79.2	0.01	0.11	1.0		20		348	99	
Wheat, whole	11.8	1.5	71.2	0.05	0.32	5.3	108	190		316	98	
Wheat flour refined	11.0	0.9	4 1	0.02	0.09	1.0		40		349	99	67
Cholam (*Sorghum vulgare*)	10.4	1.9	74.0	0.03	0.28	6.2	136	115		353	101	83
Ragi (*Eleusine coracana*)	7.1	1.3	76.3	0.33	0.27	5.4	70	140		315	98	89
Maize tender	4.3	0.5	15.1	0.01	0.10	0.7	42		4	82	23	60
Lentil (masur dal)	25.1	0.7	59	0.13	0.25	2.0	450	150		310	98	41
Red gram (thar dal)	22.3	1.7	57.2	0.14	0.26	8.8	220	150		333	95	74
Soya-bean	43.2	19.5	20.9	0.21	0.09	11.5	710	300		432	125	64
Amaranth tender	4.9	0.5	5.7	0.50	0.10	21.4	2,500 11,000	10	173	47	13	72
Brussels sprout	4.7	0.5	9.2	0.05	0.08	2.3	210		72	60	17	
Cabbage	1.8	0.1	6.3	0.03	0.05	0.8	2,000	50	124	33	9	78
Celery	6.0	0.0	8.6	0.23	0.11	0.3	6,000	T	63	64	18	
Lettuce	2.1	0.3	3.0	0.05	0.03	2.4	2,200	90	15	23	7	
Spinach	1.9	0.9	1.0	0.08	0.01	5.0	3,000	70	48	32	9	
Carrot	0.9	0.1	10.7	0.08	0.03	1.5	3,000	60	3	47	13	
Onion large	1.2	0.1	11.0	0.18	0.05	0.7		40	11	51	14	

TABLE H—*concld*

Name of foodstuff	*Protein %*	*Fat %*	*Carbohydrate %*	*Calcium (Ca) %*	*Phosphorus (P) %*	*Iron (Fe) mg %*	*Vitamin A I U per 100 g*	*Vitamin B₁ I U per 100 g*	*Vitamin C mg per 100 g*	*Calories per* 100 grammes	*Calories per* ounce	*Biological value protein*
Potato	1.6	0.1	22.9	0.01	0.03	0.7	40	20	17	99	28	67
Sweet potato	1.2	0.3	31.0	0.02	0.05	0.8	10		24	132	37	72
Tapioca	0.7	0.2	38.7	0.05	0.01	0.9		15		159	45	
Sago	0.2	0.2	87.1	0.02	0.01	1.3				351	100	
Cashew nut	21.2	46.9	22.3	0.03	0.45	5.0	100			596	169	72
Coconut	4.5	41.6	13.0	0.01	0.24	1.7	T	15	1	444	126	88
Ground-nut	26.7	40.1	20.3	0.05	0.39	1.6	63	300		549	156	88
Apple	0.3	0.1	13.4	0.01	0.02	1.7	T	40	2	56	16	
Banana	1.3	0.2	30.4	0.01	0.05	0.4	T	50	1	153	43	
Mango ripe	0.6	0.1	11.8	0.01	0.02	0.3	4,800		13	50	14	
Orange	0.9	0.3	10.6	0.06	0.02	0.1	350	40	63	40	14	
Papaya, ripe	0.5	0.1	9.5	0.01	0.01	0.4	2,020		46	40	11	
Tomato ripe	1.0	0.1	3.9	0.01	0.02	0.1	320	40	32	21	6	
Beef (muscle)	22.6	2.6		0.01	0.19	0.8	59	50	2	114	32	98
Egg (fowl)	13.3	13.2		0.06	0.22	2.1	2,200			173	49	94
Milk (cows)	3.3	3.6	4.8	0.12	0.09	0.2	180	17	2	65	18	85
Milk (skimmed)	2.5	0.1	4.6	0.12	0.09	0.2			1	29	8	
Cheese	21.1	25.1	6.3	0.79	0.55	2.1				348	99	
Red-palm oil		100.0					40 000			900	256	
Yeast, dried	30.5	0.8	39.1	0.44	1.49	43.7	110	2,000		320	91	

patients are put on to good hospital diet and their persistence if the same patients are treated in their own homes But he again finds it difficult to show any proof that these same people would not have suffered the various infections malaria amœbiasis kala azar enteric or ankylostomiasis, that probably brought them into hospital whatever their diet had been There is little indication that either the incidence or the course of the disease in the cases of smallpox, plague kala azar sleeping sickness or yellow fever i affected by the patient's state of nutrition cholera epidemic typhus and louse-borne relapsing fever are often associated with famine conditions but in these instances the rapid spreading of the disease is in part at least due to the indifference to personal hygiene that is not unnaturally exhibited by starving people. The effect of malnutrition as a predisposing cause of leprosy is a controversial subject but the consensus of opinion at present is against any association Similarly malariologists have for many years stressed the vicious cycle malnutrition—malaria—malnutrition but recently this doctrine has been questioned and some of the leading malariologists take the view that the association between malaria and malnutrition is not due to a cycle of events but to the sequence malaria—debility—poverty—malnutrition. The present writer visualizes the sequence as malaria—malnutrition—debility—poverty—further malnutrition for while admitting that the well nourished are just as susceptible to malaria and that in them the primary attack is likely to be as severe he does not believe that the true picture of chronic malarial cachexia is seen except in the ill nourished. About the association of tuberculosis and malnutrition there is little doubt The standard example is Germany in the last war here the incidence rose rapidly almost certainly as a result of the widespread malnutrition from which the whole population suffered Finally though it seems doubtful if malnutrition could determine specific dysentery infections there are certainly many non-specific intestinal fluxes that are caused by defective dietary (*vide supra*)

Some relevant data can be obtained from famine reports In India, Nicol (1940) reporting on the Hissar famine of 1938 and 1939 showed that there was no increase of malaria or of the diseases frequently epidemic in that district *e g* smallpox and cholera, but that there was a marked increase in tuberculosis pneumonia and in other respiratory diseases of over 75 per cent and an increase in dysentery and diarrhœa of nearly a 100 per cent The increase in enteric morbidity is a little harder to understand though one would certainly expect an increase in mortality The total number of deaths in 1939 are 37 707 as compared with 20,910 in 1937 The increase in the death rate was most marked in the under ten years age group and of the total deaths in 1939 21 100 were in this age group that is 56 per cent of all deaths in Hissar were in children under 10 years of age This is in keeping with the well established fact that the effects of malnutrition are most noticeable in infants and young children. Forty nine per cent of all deaths in British India as a whole were in children under 10 years of age if these figures are compared with that for Hissar (56 per cent) and England and Wales (12 per cent), it will be seen that the figure for British India is much nearer to that of the famine area than to that of England and Wales The deduction is obvious

The *recorded* infantile mortality in British India in 1939 was 155 per 1,000 live births the *actual* infantile mortality probably being much greater Another special group in which the death rate is very high is amongst pregnant and parturient women Maternal mortality has been variously estimated in different large areas in India as from 10 to 25 per mille and in one investigation in Assam an average figure of 42 was given with for one group the extraordinary figure of 137 per 1 000 births

(Balfour, 1927), this has to be compared with 2.82 for England and Wales in 1939 Neal Edwards (1940) found that 23.3 per cent of the maternal deaths in Calcutta were due to anæmia whereas anæmia was also a contributory cause in many more cases, and Napier and Neal Edwards (1941) considered that the main cause of this anæmia was dietetic

All this points to the fact that malnutrition is an important factor in the production of ill health and high mortality in India For other tropical countries e g for Java by de Haas (1939 and 1940) similar figures have been produced and the writer believes that it is fair to assume that much of the ill health in the tropics is due to malnutrition amongst the native inhabitants

Special effects

Starvation—A person who for any length of time eats less than the amount that may be considered his minimum requirements is being starved. The result of starvation is the loss of the body fat, first the adventitious fat e g the subcutaneous fat of the abdominal wall and the fat in the omentum and then the supporting fat in other parts of the body The next call is on the muscle the skeletal muscle followed by the unstriped muscle of the viscera e g of the bowel and eventually the heart In partial starvation after the fat which can be looked upon as a natural reserve has been used up the subject becomes lethargic and all muscular effort is reduced to a minimum, after which there is a slowing down of metabolism, evidenced by a fall of pulse and respiration rate until a point of compromise is reached, probably in an adult at about one thousand calories daily intake (it will be relatively higher in a child who requires some food for body building purposes) If the intake falls below this, vital organs will be affected and the subject will eventually die In complete starvation specific deficiencies do not usually develop, but in partial starvation, these may complicate the picture and hurry the end scurvy (vitamin C deficiency) is a common disease during famines

Protein deficiency—This may be (a) an absolute deficiency as in starvation, (b) a relative deficiency as in pregnant and lactating women and growing children whose protein requirements are relatively far greater than those of adult men, (c) due to the unsuitability of the protein e g zein of maize or (d) due to the defective powers of assimilation of the individual

This is the specific deficiency most commonly associated with starvation and œdema which is one of the earliest manifestations is often referred to as famine dropsy the condition is likely to occur when the protein intake falls below 30 grammes daily There is hypoproteinæmia the deficiency is mainly in the serum albumin fraction The œdema is usually confined to the legs but the whole body may be involved. There is also polyuria and some anæmia but most of the other symptoms that may be associated can probably be attributed to the general starvation. There is of course no ætiological association between 'famine dropsy' or 'war œdema' as it is sometimes called and epidemic dropsy (vide infra)

Hypoproteinæmia may occur in late pregnancy and is sometimes associated with anæmia, it occurs in women on a diet which is low in protein and although well above the 30-gramme level is insufficient to meet the additional demands

Vitamin A deficiency—This would appear to be one of the most common defects in tropical diets partly on account of the low fat intake and it is surprising that there are not more definite clinical defects attributable to this deficiency Vitamin A was at one time known a the anti infective vitamin and it was thought to be an important factor in

preventing minor respiratory infections although the case has never been very satisfactorily proved it is generally accepted that it is an important dietary factor for maintaining general health especially in children The vitamin A deficiencies most commonly encountered in the tropics are night blindness, xerophthalmia phrynoderma and possibly certain types of stone in the kidney Some of the eye conditions hitherto attributed to vitamin A deficiency have recently been shown to respond better to riboflavin than to vitamin A administration, it seems possible that the action is synergistic and that both should be given

Night blindness—The association of night blindness and vitamin A deficiency is so well established that light adaptation tests with an apparatus known as a biophotometer are employed as one of the standard methods of testing for vitamin A deficiency Inability to see at all in a dim light is a common defect in poor populations in the tropics the condition is often associated with other vitamin A deficiencies and with anæmia producing diseases *e g* hookworm disease and malaria This fact led the writer to believe that this deficiency was an ætiological factor in certain types of anæmia a belief that he was never able to establish Bright sun light also plays a part in production of night blindness (*see* p 46)

Xerophthalmia—This condition of dryness of the conjunctiva is indicated in its earliest stages by the appearance of Bitot s spots white exudative plaques or spots it may lead to keratomalacia softening and ulceration of cornea Keratomalacia is one of the commonest causes of blindness in some tropical countries *e g* southern India

Phrynoderma.—Nicholls (1933) in Ceylon Loewenthal (1933) in East Africa and Frazier and Hu (1934) in China reported a follicular hyperkeratosis particularly on the extensor surfaces of the arms and legs which they associated with vitamin A deficiency Nicholls gave the condition the name phrynoderma on account of the similarity of the condition to toad s skin which is a very apt comparison The condition is very common amongst children in several parts of India

Renal calculi—McCarrison produced renal calculi in rats by feeding them on a diet deficient in vitamin A and has suggested that the urinary lithiasis that is common in some parts of India might be due to vitamin A deficiency

Prevention and treatment.—All these conditions can be prevented by increasing the intake of articles rich in vitamin A these are leafy vegetables (*e g* spinach cabbage celery amaranth leaves and coriander leaves) carrots fruits (particularly mango and papaya) liver eggs, and butter Vegetable oils contain no vitamin A with the exception of red palm oil which contains large amounts of provitamin A or carotene which is converted into vitamin A in the body

Medicinally the best substance to give is halibut liver oil as this contains very large amounts of vitamin A one drop contains several thousand units (I U) Cod liver oil is also rich in this vitamin but has to be taken in slightly larger doses a drachm and a half will provide an adequate daily dose of vitamin A The latter oil although not so rich in vitamin A contains large amounts of vitamin D and has other nutritional qualities which make it preferable During the war the cod liver oil has been difficult to obtain and several substitutes have been tried shark liver oil has proved very satisfactory Many commercial concentrates are also available The normal daily requirements of vitamin A probably do not exceed 5,000 I U but at least 25 000 I U should be the aim in treatment and even then response may be slow

Vitamin B_1 deficiency—This vitamin has recently become a popular panacea and is at present grossly abused by the over-enthusiastic but it

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Xerophthalmia.—This condition of dryness of the conjunctiva is indicated in its earliest stages by the appearance of Bitot s spots white exudative plaques or spots it may lead to keratomalacia softening and ulceration of cornea Keratomalacia is one of the commonest causes of blindness in some tropical countries e g southern India

Phrynoderma—Nicholls (1933) in Ceylon Loewenthal (1933) in East Africa and Frazier and Hu (1934) in China reported a follicular hyperkeratosis particularly on the extensor surfaces of the arms and legs which they associated with vitamin A deficiency Nicholls gave the condition the name phrynoderma on account of the similarity of the condition to toad s skin which is a very apt comparison The condition is very common amongst children in several parts of India

Renal calculi—McCarrison produced renal calculi in rats by feeding them on a diet deficient in vitamin A and has suggested that the urinary lithiasis that is common in some parts of India might be due to vitamin A deficiency

Prevention and treatment—All these conditions can be prevented by increasing the intake of articles rich in vitamin A these are leafy vegetables (e g spinach cabbage celery amaranth leaves and coriander leaves) carrots fruits (particularly mango and papaya) liver eggs, and butter Vegetable oils contain no vitamin A with the exception of red palm oil which contains large amounts of provitamin A or carotene which is converted into vitamin A in the body

Medicinally the best substance to give is halibut liver oil as this contains very large amounts of vitamin A one drop contains several thousand units (I.U) Cod liver oil is also rich in this vitamin but has to be taken in slightly larger doses a drachm and a half will provide an adequate daily dose of vitamin A. The latter oil although not so rich in vitamin A, contains large amounts of vitamin D and has other nutritional qualities, which make it preferable During the war the cod liver oil has been difficult to obtain and several substitutes have been tried shark liver oil has proved very satisfactory Many commercial concentrates are also available. The normal daily requirements of vitamin A probably do not exceed 5 000 I U but at least 25,000 I U should be the aim in treatment and even then response may be slow

Vitamin B deficiency—This vitamin has recently become a popular panacea and i at present gros ly abu ed by the over-enthu iastic but it

does certainly appear to have a beneficial effect in a large variety of conditions, e.g. in the polyneuritis of alcoholism, pregnancy and senility, and also in cases of neuritis of doubtful origin, in cardiac failure of obscure origin with hypertrophy, in oedema, and in anorexia and function disorders of the intestinal tract due to lack of tone. As the diets of rice-eating people are very liable to be deficient in this vitamin, it is probable that many of the conditions, of the nature of those mentioned above, from which they may suffer *can to some extent be attributed to vitamin* B_1 *deficiency*, but the only definite syndrome associated with this deficiency is beri beri; this disease will be discussed separately. *The prevention and treatment of this* deficiency will be discussed under BERI BERI.

Vitamin B_2-complex *deficiency*.—This is a common deficiency in the tropics. Many fractions of this vitamin have been identified. The quantitative occurrence of each fraction has not been so thoroughly worked out as in the case of other vitamins, but as a general rule liver, brewer's yeast, certain green vegetables, pulses, meat, fish and poultry are the richest sources. Vitamin B_2 complex *occurs in large amounts in dried brewer's or* in autolysed yeast, and these are the best medicinal sources. It will be best to consider the effects of these different fractions separately.

Nicotinic acid or niacin deficiency is an important, even if not the main, factor in the ætiology of pellagra (*vide infra*); it also plays some part in the production of non-specific gastro-intestinal disturbances, e.g. sprue (*quod vide*), and toxic psychoses and encephalopathy. As our experience widens, it will probably be found that there are many other minor health defects, especially skin conditions, commonly encountered in the tropics which can be attributed to niacin deficiency.

Riboflavin.—Evidence of the deficiency of this fraction is much more frequently encountered than that of niacin; the main clinical evidence of ariboflavinosis is glossitis, cheilosis, angular stomatitis and certain eye changes, namely, congestion of the sclera, vascularization and later ulceration of the cornea, and blepharospasm, associated with photophobia, visual fatigue, dimness of vision, a burning sensation and a feeling of roughness of the eyelids.

There is superficial denudation and redness at the line of closure of the lips, maceration, fissuring and a yellowish crust formation at the angles of the mouth, seborrhoeic dermatitis around the alæ nasi and just inside the nose, at the canthi of the eyes, and on the ears, and deep magenta coloration and fissuring of the tongue and swelling and flattening of the papillæ, or the tongue may show oval or irregular areas of desquamation with atrophic centres and raised pinkish edges. These mouth changes are associated with soreness and burning of the tongue and lips and dysphagia. The subjective eye symptoms often precede the glossitis and angular stomatitis, but it may be necessary to ask leading questions to elicit the fact; they also disappear first under treatment. There is immediate response to parenteral riboflavin in doses from 5 to 15 milligrammes; with smaller doses, e.g. 3 mg., the response is still definite but it takes several days to become fully established.

The position of pyridoxin (vitamin B_6) in human metabolism is not yet fully understood, but certain nervous symptoms, including irritability, insomnia and muscular weakness, rigidity and painful spasms, and cheilosis in pellagra patients, myasthenia and muscular dystrophies, chilblains and certain forms of anæmia have improved on the administration of pyridoxin in doses of 10 to 50 milligrammes. In rats at least, this vitamin appears to play some part in the metabolism of unsaturated fatty acids, and it is suggested that its action may be similar in man and that its deficiency is one of the causes of sprue.

There are several other fractions included in the vitamin B_2 complex some of which have been identified e g pantothenic acid but the only other common tropical syndrome associated with deficiency of vitamin B_2 complex is tropical macrocytic anæmia the evidence that this is associated with vitamin B_2 deficiency is dependent on epidemiological data and on the therapeutic test that is to say the response to the administration of autolysed yeast extracts (marmite or vegex) and other substance rich in this vitamin. It has been shown that the isolated vitamins, thiamin (B_1) niacin riboflavin pantothenic acid and pyridoxin (B) have no effect on this condition

Tropical macrocytic anæmia occurs in men and women living on a poor diet in the former it is often associated with pregnancy, and in both sexes with chronic malaria Although there is little doubt that deficiency absolute or relative of some fraction—as yet unidentified—of the vitamin B complex is an important ætiological factor there are probably other nutritional deficiencies e g protein or some specific amino-acid concerned and other factors The writer has suggested that it may be a conditioned toxicity

Vitamin C deficiency —Scurvy (vide infra) and sub-scurvy degrees of vitamin-C deficiency are common in tropical countries particularly amongst labour forces working away from their home surroundings and familiar fruits and vegetables and during times of famine

Scurvy is the only definite disease associated with this deficiency but in many tropical conditions e g anæmias and intestinal disorders improvement is delayed unless sufficient vitamin C is given

The prevention and treatment of this deficiency will be discussed under the heading of scurvy

Vitamin D deficiency —Despite the fact that many tropical dietaries are deficient in vitamin D only under very special circumstances does frank rickets occur in the tropics as the hours of sunshine are many and the majority of people spend much of their time in the open air However minor degrees of rickets do occur amongst the children of both natives of the orthodox classes who do not allow their children sufficient freedom and of sojourners who are too assiduous in protecting their children from the sun

There is an adult form of rickets which is common in northern Indian towns in particular but which also occurs in other countries amongst women who are kept in *purdah* *especially when their diet is deficient in* calcium. This condition known as osteomalacia, is usually first noticed when the woman is pregnant and her calcium is further depleted by the inexorable demands of the fœtus There is softening and bending of the bones particularly those of the pelvis so that parturition becomes difficult or even impossible The first symptoms are general weakness and girdle pains there may also be tetany The condition usually becomes worse with each succeeding pregnancy if the woman survives the earlier pregnancies and no preventive measures are taken

The first *preventive* measure is education and the alteration of unhygienic social habits Otherwise it consists in seeing that all pregnant women get a sufficiency of food rich in vitamin D calcium and phosphorus and a regular period of exposure to sunlight *Treatment* by appropriate feeding and the giving of vitamin concentrates will be effective only if it is given in the early stages before the bone deformities have become established Vitamin D occurs in milk and butter (from pasture fed cattle) liver and fish liver oil The last named are the richest source Cod or shark liver oil and the pure vitamin calciferol or some proprietary

In the treatment of his own patients the doctor has a special responsibility He should always ensure that his patient's diet is adequate in all the vitamins, remembering that the requirements in the febrile conditions in particular may be above those of a normal person He should be specially cautious when his patient is subsisting on a milk diet, which is almost devoid of ascorbic acid and iron, and very low in niacin, and when nutrition is maintained largely by intravenous glucose, in which case *thiamin* will be an additional requirement.

Special problems such as that of rice and measures directed against specific deficiencies are discussed under the appropriate deficiency disease

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BERI BERI

INFANTILE BERI BERI

BERI BERI

Definition —Beri beri is a metabolic disorder characterised by peripheral neuropathy, myocardial weakness and frequently œdema occurring in persons on a diet deficient in vitamin B_1

Historical.—The syndrome known as kakke or leg disease was described in early Chinese literature several hundred years before the Christian era. The name *beri-beri* appeared later and seems to have been derived from a Malayan word biribi, meaning a jerky gait or from an Indian word *bharbari* meaning a swelling. In Japan it was known by the Chinese name *kakke* and was described by early Japanese medical writers. Bontius referred to it as occurring in the Dutch East Indies in 1642 and early English writers on tropical medicine reported it in India and Africa. The first references to the disease in the western hemisphere appeared about the middle of the nineteenth century when it was reported in Brazil and later in the West Indies.

EPIDEMIOLOGY

Geographical distribution —The disease has no geographical limitations. It was for many years looked upon as a purely tropical disease but this was shown to be a wrong conception by an outbreak in Newfoundland and since then isolated cases have been reported in nearly every country in the world. However as at least 90 per cent of cases occur amongst rice-eating people the distribution of the disease is mainly tropical the largest number of cases have been reported from China Japan (an annual average of 17,000 deaths between 1920–29) Indo-China Siam Malaya and the Dutch East Indies the Philippines India tropical and South Africa also Brazil and the West Indies. Small outbreaks have occurred amongst the natives of Western Australia in Newfoundland and Labrador in Iceland and in institutions in the United States Great Britain, France and Holland.

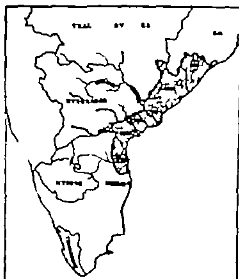


Figure 172 Map showing distribution of beri-beri in southern India in 1938 and the number of cases of beri-beri treated in each district during that year (Aykroyd *et al.*, 1940)

In India, some confusion has arisen through the popular practice (which is unfortunately sometimes encouraged by medical writers) of referring to epidemic dropsy as beri beri but it is now generally accepted that the only area where the beri beri assumes serious proportions is in the north east coastal area of the Madras Presidency the Northern Circars (*see* figure 172)

Epidemic status —It is not a truly epidemic disease (*see* p 325), but the appearance of outbreaks that involve a large number of persons living in close contact and of course always on the same diet give the semblance of an epidemic. Nor as far as is known is it in any way dependent on local conditions except in so far as these affect the food supply of the population. As noted above, it occurs mainly in native populations whose staple food is milled rice. It has also appeared in armies labour forces and amongst the inmates of institutions similarly fed, and has disappeared when the diet has been changed to under milled rice or some suitable supplement has been added. Outbreaks not associated with milled rice have been reported amongst people who have lived for some time on a monotonous diet with white flour as the staple substance *e g* in New

foundland where the diet was almost solely white bread and molasses for certain months of the year and in institution usually mental asylums where white bread was used It has also occurred on ships where ships biscuits made from white flour and tinned food have been the principal diet.

It is a disease of towns rather than rural areas

Seasonal incidence —In most places where the disease occurs there is some season during which it is most prevalent but this is not by any means the same season in different places Much capital has been made out of this seasonal incidence by the champions of different theories, who can usually find from the varied data some that suit their particular theory For example in the Godavari delta (Southern India) the incidence of beri beri is high in September and low in January this no doubt would be attributed to the stored rice becoming damp during the monsoon by the supporters of the rice-infection or rice-toxin theories but Aykroyd and Krishnan (1941) find quite a different explanation namely that when the rice is freshly harvested at the end of the year it is not suitable for consumption unless it is first parboiled so that in this district 56 per cent of the rice eaten in January is parboiled whereas in September the last year s crop is mature and can be eaten without previous parboiling and only 6 per cent of rice eaten in this month is parboiled In nearly every case the seasonal incidence can be similarly explained in terms of the present theory of the ætiology of the disease (*vide infra*)

Age sex and race incidence —In a mixed population the disease is undoubtedly less common in children than in adults though it does occur amongst the former There is also a form of infantile beri beri that occurs in the breast fed infants of mothers with beri beri More men than women are affected but there is little evidence of any true sex preference except that possibly in the working labourer the caloric requirements are greater he will eat more rice his vitamin B requirements will be correspondingly greater and he is therefore more likely to show evidence of the deficiency The more probable explanation is however that there are usually more men than women in the type of population that is affected

There is little evidence that any one racial type is more susceptible than any other the fact that European personnel of institutions escape the disease when native soldiers or native inmates suffer can of course be explained on the differences in their dietary

ÆTIOLOGY

Historical.—The story of the discovery of the cause of beri-beri forms an important part of the story of the discovery of the vitamins

The first worker to recognize the dietetic nature of beri-beri was Takaki. In 1884, he recommended the replacement of the rice diet in the Japanese navy by a mixed diet that included wheat bread fresh vegetables and milk, and this disease which had been responsible for sickness amongst at least 25 per cent of the navy s personnel every year previous to 1884, had disappeared entirely by 1887

In 1890 and the two succeeding years, Professor Eijkman, working in a laboratory in Batavia that had been established for the study of beri-beri, produced polyneuritis in fowl by feeding them on polished rice and cured it by giving them an alcoholic extract of rice polishings He did not suggest that the disease he had produced was true beri-beri but the inference was obvious. Professor Grijns who succeeded him in Batavia carried the work further and came to the conclusion that beri-beri was due to the absence of some essential ingredient from the food. As a result of the recommendation of these two workers beri-beri was largely controlled in the Dutch army and in government institutions in Java

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P rboiling ves the t in Ik P I

In 1907 Fletcher carried out some important epidemiological observations at the Kuala Lumpur mental asylum which showed that the *disease* occurred amongst those that ate 'uncured' polished rice but not amongst Indians, who ate 'cured', that is parboiled rice, or amongst Malays who pounded their own rice (*for the significance of these observations* see p 717 of the previous chapter).

In 1909 Fraser and Stanton carried out some planned feeding experiments with Javanese labourers they confirmed the above observations, but also *showed*, by interchanging the experimental groups, that locality had no influence on the development of the disease and that it was not transmissible from one man to another. They also carried out experiments with fowls that showed, in addition to the facts already elicited by previous workers, that storage in a damp place had no detrimental influence on rice, *vis-à-vis* beri-beri but that if the whole rice grain was subjected to autoclaving at 120° C for an hour it would produce 'polyneuritis' in birds in exactly the same way as polished rice this experiment incidentally also showed that no *living infective* agent in the rice was responsible for the disease. Other confirmatory experiments were carried out by Strong and Crowell (1912) and by Vedder. Casimir Funk, working at the Lister Institute, isolated a protective substance from rice polishings in 1911 and introduced the word 'vitamine' from which the 'e' was afterwards dropped. The pure crystalline vitamin B_1 was chemically identified in 1926, by Jansen and Donath, and synthesized by Williams and his co-workers in 1936.

Many other theories were advanced regarding the nature of beri-beri. Several *so-called* causal organisms were isolated, and the theory that badly-stored rice developed some special toxin was strongly supported, although this last theory still has advocates even to-day most of the other theories have in turn given way to the vitamin-deficiency theory. The fact that there are two clinical types of the disease, the wet and the dry has led Vedder (1940) to suggest that vitamin B_1 *may be divided into two parts, the x fraction deficiency of which is responsible for the dry form* and the *fraction y* deficiency of which is responsible for the wet form. The suggestion is an interesting one but awaits biochemical confirmation further it is not entirely necessary to explain the facts (*vide infra*).

The present position.—It is generally accepted to-day that the essential ætiological factor in the syndrome beri beri is a deficiency absolute or relative of vitamin B the pure form of which is known as thiamin or aneurin. *Whenever the disease has occurred* in a community it has been possible to show that the staple food was milled rice or some other cereal which in its preparation had been deprived of the bulk of its natural vitamin B_1 alteration of the diet so that it includes an adequate amount of this vitamin has always led to the disappearance of the disease from that community and administration of large doses of the vitamin will always cause a disappearance or at least marked improvement in the specific symptoms of individual sufferers.

In a community in which there is a low intake of vitamin, the individuals most likely to suffer from beri beri will be those who take an exceptionally large amount of carbohydrate, pregnant and lactating women, hyperthyroid individuals and subjects with febrile diseases *all of whose* normal requirements of vitamin B_1 are increased.

Sporadic instances of beri beri, if they cannot be *explained on the* grounds of actual deficiency of vitamin B in the food taken as in the case of long-continued dietary restriction or of *chronic alcoholism* when the appetite is dulled and alcohol itself acting as a pure carbohydrate *provides a large proportion of the calories can be* traced to malabsorption or faulty storage and utilization as for example in achlorhydria and *chronic* digestive disorders or in cirrhosis and other diseases of the liver these are sometimes referred to as secondary beri beri.

Thus to summarize the causes of this disease are (*a*) absolute deficiency of vitamin B_1 in the diet (*b*) a deficiency relative to the special requirements of the individual, (*c*) failure of absorption of vitamin B and (*d*) failure of storage and utilization.

It is frequently claimed especially by workers who *still* have a leaning towards some of the earlier discarded *theories that the deficiency* of vitamin B_1 is not the whole story of the ætiology of beri beri. This is

of course very probable one might almost say quite certain as what single ætiological factor is the whole story of any disease ? In an infectious disease there is always the seed *and* the soil to be considered similarly in an induced metabolic dysfunction both the patient's previous metabolic state and superimposed infections may well help to determine morbidity Further it is probable that if one vitamin is deficient others will also be deficient and these other deficiencies may contribute to the clinical picture. And having decided that it is purely an avitaminosis do we know how a deficiency produces a disease, and can we entirely discard the possibility that this vitamin and perhaps other vitamins act by counteracting the effect of some noxious product of metabolism ? In fact, infantile beri beri (*vide infra*) that occurs amongst suckling infants of mothers with beri beri provides some evidence that this may be the case

Vitamin B_1 requirements —The figure usually given is 330 to 660 international units (I U) or 1 to 2 milligrammes The higher figure will include such special classes as pregnant and lactating women However it has recently been shown that the vitamin B requirements vary according to the carbohydrate intake and it is now usual to express the vitamin B_1 requirements in terms of the calorie intake it is suggested that the lowest safe amount is 0.25 I.U per calorie (Williams and Spies 1938) which in the average man will be above the maximum indicated above However when most of the calories are from carbohydrates this figure will not be too high. Fat spares vitamin B_1 and when the latter is deficient the body fat is drawn upon to reduce carbohydrate metabolism to a minimum when this vitamin is exhausted carbohydrate metabolism increases and symptoms of beri beri soon appear It usually takes three months on a deficient diet before the vitamin B_1 reserves in the body are exhausted and the full syndrome is established although in human experiments Williams and others (1943) showed that on a daily diet of 2,000 calories and 0.35 mg. of vitamin B (= about 0.06 I U per calorie) the earliest symptoms appeared in 30 days

The work of Mills (1941) with rats suggests that tropical conditions may increase the requirements of vitamin B This is interesting in view of the fact that beri beri is more common in tropical countries but it should be confirmed with other animal species and by human experiments in view of the contradictory fact that tropical heat reduces basal metabolism

Sources of vitamin B —The best sources of this vitamin are pork *whole-grain cereals and their products beans and peas yeast and liver* Although milk meat other than pork and fruit do not contain much vitamin B_1 it is present in small quantities in most natural foodstuffs. It is however often discarded or destroyed in the preparation of these for consumption *e g* in the milling rice and other cereals in cooking and in canning It is destroyed by heating to 130 C in one hour It however withstands boiling in an acid medium but is destroyed in an alkaline medium.

Recent work (Najjar and Holt 1943) suggests that in certain circumstances thiamin may be synthesized in the human intestinal canal. The implications of this observation are very great and although it is not clear what determines the synthesis it seems likely that the nature of the staple diet, or of other non vitamin dietary factors may have some influence

For further details regarding the source of this vitamin the reader is referred to the tables and the discussion on rice in the previous chapter

PATHOLOGY

Morbid anatomy —The whole body is wasted and all subcutaneous fat has disappeared this may be masked by œdema. There may be

generalized *œdema* with fluid in the serous cavities. This œdema is not necessarily due to cardiac failure as it often occurs in a person with a competent heart, but to a breakdown in the mechanism that controls the interchange of fluids and maintains the water balance of the tissues It is more marked in the more acute cases The changes in the peripheral nerves are degenerative rather than inflammatory, so that the word *neuritis* is inappropriate The nerves of the legs are first affected, mainly the sciatics and their branches, then those of the upper limb and more rarely the cranial nerves and the sympathetic system. The nerve lesions vary in their extent according to the severity and duration of the affection there may be barely detectable microscopic lesions degeneration of the myelin sheath only the axis cylinders remaining intact or with degeneration of some of the axis cylinders or complete degeneration and death of the whole nerve

As well as the peripheral nerves scattered fibres in the tracts cells of the anterior and posterior horns and the sympathetic ganglia are affected. The muscles supplied by the affected nerves show atrophic changes. There is hypertrophy and dilatation particularly of the right side of the heart. (This dilatation may be sudden and is often associated with heart failure and death.)

Microscopically the most striking feature is intercellular œdema. There is also fragmentation, fatty and hydropic degeneration and rarely necrosis of the cells. (The heart failure is due to this water retention with its effect on the cells of the myocardium more than to vagal neuropathy but it is possible that both factors operate)

Biochemistry —Vitamin B_1 is absorbed in both the small and the large intestine It is stored in the liver and kidneys but it is also found in other organs and tissues It is excreted in the urine, and the amount excreted is a good indication of the vitamin B_1 state of the organism in health the average daily excretion in an adult is 20 to 30 I.U being higher in men and this may fall as low as 3 5 I.U in beri beri The vitamin-B content of the blood in the normal persons $9 \pm 2\chi$, or about 2 to 4 I U per 100 c.cm. of blood the blood content is not a good indication of saturation as it may be normal in beri beri All evidence goes to show that vitamin B_1 acts as a co-enzyme in the metabolism of carbohydrate, and controls the oxidation of some intermediate product It is certain that the vitamin B_1 requirements vary according to the carbohydrate intake. It is suggested that this intermediate product is (at least in the case of some carbohydrates *e g* rice) of a toxic nature.

It has been found that the pyruvic acid in the blood and body tissues varies inversely with the vitamin B_1 intake The normal level of pyruvic acid in the blood is 0.5 to 1 0 mg per 100 grammes it rises considerably in acute cases of beri beri but is restored to normal by vitamin B administration In more chronic cases it may be demonstrably increased. A sharp and prolonged rise in the blood pyruvic acid after intravenous glucose constitutes a useful test for vitamin B_1 deficiency

The urine —This will not show any characteristic changes. It will be scanty and there may be anuria during the severe cardiac attacks On resumption of the flow there will be a heavy cloud of albumin and granular casts The vitamin B content has been discussed above

The blood picture —There is often a marked macrocytic anæmia. Although this may be due to associated deficiencies the writer has seen cases in which the anæmia appeared to respond specifically to thiamin chloride injections The lymphocytes are reduced and in the infantile form, small lymphocytes may be absent.

SYMPTOMATOLOGY

Introduction.—The beri beri syndrome is a clear-cut one, quite distinct from any other recognized syndrome but nevertheless as in almost any disease there are distinct clinical types the distinction being due to the predominance of different symptoms which in turn are dependent to some extent on the speed of onset of the dysfunction In most outbreaks all types will be represented but frequently one type will predominate and give the outbreak its special character This fact has led Vedder to believe that there are two fractions in vitamin B either of which may be deficient (*vide supra*) although this is a possible explanation it is not entirely necessary in order to fit the facts

The three main types described are (*a*) the acute fulminating cardiac form (*b*) the less acute œdematous or wet form and (*c*) the more chronic polyneuropathic or dry form The acute fulminating form is usually fatal, but if the patient recovers from the wet form he may pass into the chronic form. There will of course be obvious cases of beri beri that will defy accurate classification

It is usually about three months after the diet has become deficient in vitamin B that the first symptoms appear if the deficiency has been very complete, the time may be shorter

The fulminating form.—After perhaps a few days of prodromal symptoms such as anorexia gastro-intestinal disturbances easy fatiguability or in some cases without any warning the patient becomes breathless and cyanosed he complains of severe epigastric or substernal pain and often vomit he may also suffer from aphonia (the result of pressure by the right auricle on the recurrent laryngeal nerve) His heart is greatly dilated the veins in the neck stand out and the liver becomes large tender and pulsating The systolic blood pressure is usually lowered and the diastolic very low indeed The patient dies suddenly within a day or so of the first onset of symptoms with acute circulatory collapse

The œdematous form.—In this form the onset is a little more gradual after a short but definite period of ill health often with gastro-intestinal symptoms there is a gradual onset of œdema with tiredness and shortness of breath on exertion The œdema at first only in the extremities, gradually extends until it involves the trunk eventually there is general anasarca. There are usually some symptoms of peripheral neuropathy but as the other symptoms confine the patient to his bed they are easily overlooked wasting is masked by the œdema

The heart is usually dilated the apex beat is diffuse and fluttering the pulse is soft and rapid the veins in the neck are prominent the liver is enlarged and tender and the pleural cavities fill with fluid but usually the lungs remain clear until a terminal œdema develops The blood pressure falls as in the acute form with the relaxation of the peripheral tension an injection of adrenalin further lowers the diastolic blood pressure almost to zero but pitressin causes a rise in blood pressure that is maintained for an hour or so The electrocardiogram may show right axis deviation and flattening of the T waves also prolongation of the Q T interval and a low QRS complex.

The chronic polyneuropathic form.—The onset of this type is far more gradual and for some weeks the patient may struggle on with his work, complaining of loss of weight weakness slight breathlessness on exertion headache and vague pains stiffness and lameness of the legs The only objective symptom may be tachycardia. The condition increases and he becomes less able to carry on his work. He now complains of numbness and a burning sensation of the feet as well as stiffness of the legs and he finds difficulty in rising from a sitting posture the calf muscles are tender on pressure and areas of hyperæsthesia appear which later become

anæsthetic knee jerks which were at first slightly exaggerated now disappear and so do the ankle jerks The definite characteristic ataxic high stepping gait appears The condition then spreads to the upper limbs there is wrist-drop wasting of the hands and forearms, and inco-ordination of the movements of the hand so that the patient drops things easily and is unable to pick up small objects Chvostek s sign (fibrillary tremors of the muscles on being tapped) may be present.

The muscles of the limbs become wasted and show the typical reaction of degeneration The patient gradually becomes emaciated, helpless and bedridden The sphincters are usually unimpaired and the mental condition remains clear There is usually constipation indigestion and some increase of cardiac symptoms otherwise the condition of the patient remains good but he may die of hypostatic pneumonia or some other complication.

Irreversible changes take place in the nerves contractures occur in limbs and even if he lives, the patient becomes irreparably crippled.

Sporadic or conditioned beri beri* —The beri beri that occurs in well-fed populations in special individuals *e.g* pregnant women, alcoholics, etc. (*vide supra*) usually takes the chronic peripheral neuropathy form, but with recognisable cardiac signs and symptoms, and quite often a variety of other symptoms suggestive of neurasthenia However acute cardiac attacks have been reported.

Sub-clinical beri beri —Positive evidence of a fact already assumed by many workers namely that in a population in which there are many cases of beri beri there will be many other persons on the threshold of clinical avitaminosis is rapidly accumulating now that biochemical tests for this vitamin are within the scope of the medical investigator—even if not of the ordinary practising physician and there are several relatively simple clinical tests (*vide infra*) Although these minor degrees of B avitaminosis may be classed as sub-clinical if the person is examined and questioned carefully some of the minor signs and symptoms *e g* tachycardia breathlessness on exertion, anorexia stiffness and vague pains emotional instability and mental depression may be elicited.

DIAGNOSIS

This can be considered under a number of headings —

(*a*) The patient s environment diet and habits

(*b*) The clinical picture.

(*c*) Clinical tests including the therapeutic test.

(*d*) Biochemical tests

Little further need be said about (*a*) and (*b*) It is unlikely that an outbreak of œdema or neuritis in a poorly fed population would fail to arouse one s suspicion but sporadic cases very often will in fact there is evidence that until a few years ago the majority of such cases were wrongly diagnosed The conditions for which they may be mistaken are considered below

(*c*) Of the clinical tests, the most valuable is the therapeutic test but it is very liable to be misleading in that in so many conditions a

* The writer has avoided the word *secondary* because he considers it misleading and believes that eventually it will be dropped. It is extremely probable that in any outbreak of beri-beri in a population living on a diet deficient in vitamin B_1, morbidity is determined by some secondary factor in nearly every case, whether it be slight hyperthyroidism a febrile infection, *e.g* malaria, or the consumption of a larger amount of rice than the rest of the population. It would be unreasonable to consider such cases *primary* whilst labelling as *secondary* a case of beri-beri associated with pregnancy

B avitaminosis may be superimposed on some other condition so that immediate improvement on administration of thiamin chloride does not provide the whole answer conversely where there are other deficiencies besides those of vitamin B_1 the slowness of the improvement after the administration of the pure vitamin does not altogether exclude beri beri

However a few doses (ten may be considered the maximum) or even a single dose of 10 milligrammes given intravenously will often produce dramatic improvement in the leading symptoms This applies specially to the cardiac condition in the polyneuropathic form the improvement will be slower and in advanced cases of nerve degeneration there will be none.

Other tests for vitamin B_1 saturation have been suggested In a case of deficiency adrenalin will cause a further sharp fall often to zero in the already low diastolic blood pressure or as a variation the rise—if there is—in systolic blood pressure after the administration of adrenalin will be greater if a large dose of thiamin chloride has been given previously Another test is associated with the diuretic effect of thiamin in the deficient individual this is considerable. Finally the circulation time which is usually prolonged in cardiac failure is normal or decreased in beri beri.

(d) Of the biochemical tests the best indication is obtained from the excretion of vitamin B in the urine the average daily excretion in a normal person is from 20 to 30 I U and in a patient with beri beri about 3.5 I U but both figures are subject to considerable individual variation. After a test dose of thiamin at least 28 per cent is excreted in the urine within 24 hours if the patient is saturated if he is deficient the figure is much below this Neither test can be considered a practical one, but it is probable that easier and more satisfactory tests will be devised.

Differential diagnosis.—The neuropathies have to be distinguished from those of arsenic lead, triorthocresyl phosphate ('jake') and other poisons from diphtheritic paralysis from rheumatism and various myopathies from tabes dorsalis lathyrism and other brain and cord affections and from Korsakoff's syndrome and other neurasthenias. Alcoholic neuritis is not included here as it seems probable that B avitaminosis plays an important part in this syndrome.

The œdema has to be distinguished from that of kidney and organic heart disease from famine œdema and epidemic dropsy from ankylostomiasis and other helminthic infections and from many other diseases in which there is debility malnutrition, and anæmia.

In most of these conditions if the case is a typical one there are one or more characteristic signs or symptoms that will differentiate them sharply from beri beri enumeration of these does not seem to be called for here

PREVENTION

This can of course be summed up in the single sentence increase the intake of food rich in vitamin B_1 There is however more to be said on the matter than this. Let us first take the sporadic case this usually presents little difficulty In conditions such as pregnancy hyperthyroidism it is advisable to recommend the regular taking of extract of yeast or rice polishings or some medicinal form of vitamin B as well as food rich in this vitamin (*vide supra*) This also applies to patients put on to a restricted dietary for any reason In gastritis or pernicious vomiting, it is advisable to give the prophylactic thiamin chloride parenterally

The real problem is the prevention of beri beri in large and poor populations The general problem of the prevention of malnutrition has been discussed in the previous chapter and it has been suggested that

the way lies through improvement of economic status and education, but there are certain special problems connected with this disease. As was noted above over 90 per cent of beri beri occurs amongst rice-eating people. The whole edible portion of the rice grain contains quite sufficient vitamin B_1 to ensure the proper metabolism of the whole grain, but when the grain is milled in the raw state, much of the vitamin is lost, and when it is washed and cooked and the water discarded, more of the already depleted vitamin is wasted. Parboiling prior to husking saves most of the vitamin. If therefore people will first parboil their rice home-pound it instead of allowing it to be overmilled clean it—if this is necessary—in the dry state cook it with the minimum of water and utilize any rice water in their food, beri beri will not occur. In populations where milling has been established for some time there are many practical difficulties in instituting this ideal procedure which are dealt with above (see p. 717) where also a compromised procedure of limiting the degree of milling is discussed.

The same problem has to be faced in the case of other cereals the case of white flour which is also deficient in vitamin B_1 but which for æsthetic and other reasons is often preferred has been met in some countries by 'fortifying' the white loaf by the addition of synthetic thiamin chloride.

TREATMENT

The treatment can be considered under three headings specific, dietetic, and symptomatic. It may be argued that the specific and the dietetic treatment cannot strictly speaking be separated, but as in many cases it will be advisable to give thiamin chloride in addition to any special diet that is recommended as it is very often given parenterally as it is a chemical compound made synthetically in the laboratory and as it is as dramatic in its action as any specific it seems to the writer simpler to consider it as a specific drug.

Specific.—It will naturally not be possible to give thiamin chloride to every member of a large community in which the majority of the people are suffering from either frank or sub-clinical beri beri nor in a large percentage of the cases would it be necessary but in all frank cases of beri beri thiamin chloride should be given in large doses as early as possible for one can seldom be certain that the condition will not suddenly become acute. It has been shown that the best results are obtained when generous doses are given and for an adult a daily dose of at least 20 mg should be given, either intramuscularly or intravenously for ten days to a fortnight after this the dose can be reduced considerably or thiamin (10 mg.) dried brewer's yeast (6 ounces) or marmite (2 ounces) can be given by mouth. Infants can be given 3 mg. of thiamin chloride daily with safety in fact it is very doubtful if there is any limit to the dosage. In acute cardiac cases doses of over 100 mg have been recommended but the writer believes that 25 mg is about the maximum effective dose. The development of sensitivity to thiamin chloride has been reported so that there may be danger in intermittent parenteral treatment. The dose should not be spaced too widely and if treatment has to be restarted after an interval a small test dose should be given first. There is much to be said for combining the parenteral thiamin with yeast extract as the latter contains other vitamins particularly those of the vitamin B complex group that are probably also in deficit.

Dietetic.—Rice should be excluded from the diet at first, because of its high carbohydrate content but also because of the possibility that intermediate products of metabolism of the rice carbohydrates may be

especially toxic Th[illegible] p[illegible] [illegible] d be [illegible] to a diet composed of substances low in carbohydra[illegible] and h[illegible] in [illegible] min B content such a[illegible] egg yolk liver pork [illegible] peas [illegible] parsnip radishes nut and soya bean L[illegible] milk [illegible] bread or other whole-grain cereal and any substance [illegible] he normally includes in his diet may be added [illegible] tally he may be allowed to return to his rice diet bu[illegible] be un[illegible] mill[illegible] nd parboiled and the addition of vitamin B [illegible] should be recommended

Symptomatic.—In th[illegible] severe c[illegible] es the patient must be confined to bed put on a light [illegible] di[illegible] with th[illegible] fluid intake reduced to a minimum and generally treated a[illegible] a m[illegible] lical emergency Precordial pain may be relieved by applying leech[illegible] or [illegible] may be necessary to let a little blood but [illegible] blood p[illegible] should be avoided if possible [illegible] embarrassing the heart should be remov[illegible] [illegible] should be given Intravenous thiamin in large doses a[illegible] recommended above will usually produce diuresis reduce the œdema and relieve the heart [illegible] if anuria continues one of the mercurial diuretics e.g. [illegible] may [illegible] to be resorted to Digitalis and cardiac stimulants are usually of little value but strophanthus has a reputation for being particularly useful in this condition Oxygen given continuously and properly will usually r[illegible] the patient

Little can be done to relieve the neuropathy b[illegible] the specific and dietetic treatment but massage and electrical treatment will help to maintain the tone of the muscles until the nerves recover It may be advisable to use splints to prevent wrist and foot-drop

Prognosis.—In fulminant cases either adult or [illegible] is usually hopeless in any case in which there are cardiac sym[illegible] is bad but immediate and efficient treatment may save the patient and in the severe neuropathic cases permanent disability may result but in the earlier cases when only a few nerve fibres have degenerated, suitable treatment will lead to complete recovery

In the acute cardiac attack in sporadic beri beri where there is no background of long-continued vitamin B starvation there is often a dramatic response to large parenteral doses of thiamin

INFANTILE BERI BERI

Most of the evidence suggests that this disease is the same as adult beri beri, but there are special epidemiological and clinical features that make it more convenient to discuss the infantile form separately

Epidemiology.—It occurs in the infants in a population living on a diet low in vitamin B content and usually in one in which there are numerous cases of adult beri beri. The highest incidence is in the second to the fourth months of life in infants that are entirely breast fed but it also occurs in infants that are partly breast fed, or even not breast fed The mothers are usually found to be suffering from minor degrees of chronic beri beri but they may show no clinical evidence of beri beri at all. It is believed that the particularly high infantile mortality in countries subject to beri beri can be attributed to the high incidence of infantile beri beri. This has recently been emphasized by Aykroyd and Krishnan (1941a) who has carried out a survey in the [illegible] district of Madras one of the worst beri beri areas in southern India and have shown that the peak of the infantile death rate curve in this and other beri-beri districts is not a[illegible] usual at the first month [illegible] from the second to the sixth months

Ætiology.—There are two schools of thought on the [illegible] of the disease both point out that in [illegible] all [illegible] intake of

down into riboflavin nicotinic acid afterwards called niacin etc (see p 724) and Elvehjem demonstrated that niacin would cure pellagra It has been confirmed by many workers that in most cases the administration of niacin will effect a complete cure of pellagra in a very short time Niacin was first synthesized in 1879, and was isolated from rice polishings by Funk in 1911 but was discarded by him because it did not cure beri-beri

This is not however the end of the story of the ætiology of pellagra which many people still believe to be an unsolved problem, before discussing the position as it stands to-day it will be as well to review the various theories that have been put forward —

(i) *The maize infection theory*—It has been suggested that in certain cases maize is, or after defective storing in damp conditions becomes, infected and produces the disease in those who consume it, either directly, or indirectly by interfering with absorption or by causing decomposition. Although the disease appears in epidemic form amongst maize eaters, and although legislative measures aimed at controlling and improving the storage of maize have apparently reduced the incidence in the past, the disease is never transmitted to persons on a good diet, and there is little if any experimental support for this theory

(ii) *The maize toxin theory*—The neurological changes that occur appear to be of toxic rather than bacterial origin and support has recently been given to this theory by the occurrence of pellagra amongst individuals taking maize alcohol but there is no evidence experimental or otherwise to indicate the actual nature of this toxin and attempts to isolate it have failed Further many people have taken maize as their staple diet all their lives and have never suffered from pellagra, and yet others who have never taken maize suffer from it.

The constancy of the skin lesions and the fact that the general symptoms run parallel to these, improving during the cold and sunless months of the year for example has led to the suggestion that a *pre-toxin* is ingested or formed which is converted into a toxin by the action of the ultra violet rays, as ergosterol is converted into vitamin D but here again support for this theory is lacking.

(iii) *Protein deficiency*—This theory is dependent on the fact that all pellagra-producing diets are low in protein content. Maize has a low protein content compared with other cereals, and, further the biological value of the protein is also very low The two facts combined make maize a very poor source of good protein.

(iv) *Specific protein or amino-acid deficiency*.—Maize is defective in protein not only quantitatively but qualitatively and there are for example certain important amino-acids absent from maize protein or zein *e.g* tryptophane and lysine It was suggested that some such specific deficiency is the cause of pellagra.

(v) *Vitamin deficiency absence of the PP factor from the diet*—The PP (pellagra-preventing) factor is part of the vitamin B_2 complex which contains, amongst other vitamins niacin, lactoflavin or riboflavin, and pyridoxin [B_6 or anti-dermatitis (rat) factor] Food that is rich in vitamin B_2, such as yeast, meat, and liver extract rapidly cures uncomplicated pellagra, even in patients who are left on their otherwise pellagra-producing diet. More recent work, referred to above has identified niacin as the specific PP fraction, and the synthesized vitamin will control many of the specific symptoms of the syndrome

For this theory support has been obtained from animal experiment Dogs fed on pellagra producing diet develop a condition known as black tongue, this condition clears up rapidly when vitamin B_2 complex is added to the diet, and is considered to be analogous to pellagra in man It has been shown that niacin is the fraction of vitamin-B_2 complex that is specific in black tongue whereas the other fractions of vitamin-B_2 complex are not. On the other hand, it has been shown that the dermatitis produced in rats by feeding them on a diet deficient in vitamin-B_2 complex which though it has been named rat pellagra is apparently not analogous to the human disease does not respond to niacin, but improves when vitamin B_6 is given.

The present position —This can best be stated by first enumerating some of the established facts —

(*a*) Niacin in suitable doses will effect a complete and dramatic cure in most cases of pellagra but of course the condition is likely to return unless the patient changes his diet

(*b*) In other cases, niacin will improve the condition of the patient and cure his skin lesions but will effect little change in other symptoms which require for their cure the administration of other vitamin fractions, *e g* riboflavin for the cheilosis and glossitis and thiamin for the peripheral neuropathy

(c) In yet other cases of apparently typical pellagra niacin has no beneficial effect at all some of these patients respond to liver extract but others are totally refractory

(d) Analysis of foods for their niacin content has brought to light many anomalies e.g Aykroyd and Swaminathan (1940) have shown that the rice diet taken by many millions of people in India is a much poorer source of niacin than the maize diet of certain pellagrins However some workers question whether at present chemical methods of estimating niacin in foodstuffs are sufficiently accurate to base any important conclusions on such estimations.

Now observations (a) (b) and to some extent (c) could be explained on the ground that the pellagra syndrome is caused by multiple deficiencies and that supplying of the most urgent need may be sufficient to balance the metabolism of the whole body or it may not in which case other vitamins are required

The complete explanation of (c) does not seem possible on known facts and necessitates introducing a more hypothetical explanation It has been suggested that there is an intrinsic and an extrinsic factor, the latter being niacin and the former not of course the same as the intrinsic factor deficient in pernicious anæmia but closely related to it, for all pellagrins show achlorhydria or hypochlorhydria There is certainly evidence that the individual make-up of the patient e g his endocrine balance, determines to some extent the onset of pellagra in one person and not in another on a similar diet and probably also the response to treatment. Cases have been reported which suggested the existence of antagonistic action between thiamin and the PP factor (Lehmann and Nielsen 1939) The writer has recently reported a case (Napier and Chaudhuri 1943) in which pellagra was apparently controlled by means of thyroid extract. Is it possible that the antagonism lies in the fact that beri beri is associated with hyperthyroidism and pellagra with hypothyroidism ?

Observation (d) is puzzling. It seems to the writer that no explanation of the ætiology of pellagra can be accepted that does not take into consideration the past and present predominance of the disease amongst people whose staple food is maize This brings one back to the maize-toxin theory which by itself is not acceptable but yet might be reconsidered in conjunction with the vitamin-deficiency theory It is suggested that a certain amount of niacin is counteracted by the hypothetical maize toxin so that when this is present in a diet the normal requirements of niacin are increased As alternatives to the theory of a toxin produced by the effects of external agent e g bacteria on the maize grain it i possible that some intermediate product of metabolism of maize protein or maize carbohydrate is toxic or at least capable of fixing the niacin or to carry theoretical considerations further that niacin may be synthesized in the intestinal tract under certain conditions [cf the synthesis of thiamin Najjar and Holt (1943)] which a maize diet does not favour

In conclusion putting aside theoretical consideration one can say that the exact ætiology of pellagra is not yet known but that deficiency of niacin—actual deficiency in the diet deficiency relative to requirements or deficiency due to malabsorption—is the important factor that possibly another factor is associated with maize or other staple food substance and yet another with the patient s individual make-up

Niacin requirements.—The general opinion that 10 mgm of niacin is the minimum amount required daily is little more than a scientifically

Some workers deny the fact that the true pellagra syndrome er fails t espond to niacin given both orally and parenterally

along the edge and on the frenum of the tongue, and ulceration of the gums which are often infected with Vincent's spirochæte. There is increased salivation due to inability or disinclination to close the mouth over the swollen tongue. The pharynx becomes involved in the same process; this leads to difficulty in swallowing and disinclination to take food soon follows. Later, the tongue may become completely denuded of epithelium, atrophied and fissured.

The bowel symptoms are not by any means constant, but there is often a troublesome diarrhœa of the lienteric type. There is usually an anorexia, even in the absence of dysphagia, discomfort in the upper abdominal segment after food, and a persistent burning pain. There is evidence of gastritis which is associated with specific malnutrition of the mucous membranes generally, and is in keeping with the constant hypo- or achlorhydria. Through the gastroscope, the mucous membrane is a fiery red colour. There is often redness and soreness of the anus.

Nervousness.—Tremors of the tongue and face muscles are noted early in the disease and the occurrence of Chvostek's sign (a spasm of the facial muscles on tapping) has been reported; later, this extends to other muscles. There are fleeting pains in different parts of the body, numbness and paræsthesia. The deep reflexes are exaggerated at first, later decreased, and finally lost. Peripheral neuropathy is often very troublesome, but recent work tends to suggest that this may be an associated condition (vitamin B_1 deficiency).

Later mental changes are characteristic symptoms of the disease; there is headache, sleeplessness, dullness, anxiety neurosis, confused thought and depression, amounting to melancholia which quite often leads to suicide. In some cases a manic depressive syndrome has followed periods of excitement with hallucinations.

So-called toxic psychoses that develop after a febrile attack or after an operation, are apparently due to niacin deficiency and respond to parenteral administration sometimes within twenty four hours. An acute encephalopathy due to sudden complete deprivation of niacin in a depleted individual has been described.

Other signs and symptoms.—The vaginal mucosa is usually red and sore and there may be a vaginal discharge. There is nearly always progressive emaciation. There may be irregular fever but it is not a constant symptom nor is it probably associated with the central pathological and symptomatic syndrome. Anæmia is usually very noticeable; this has been mentioned above.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A typical case presents an unmistakable picture but at the other end of the scale there are cases with slight and questionable symptoms that will defy accurate diagnosis except possibly by biochemical and therapeutic tests.

Diagnosis will have to be considered under the following headings:—

(a) *History.*—Environment and diet, general and special, duration and seasonal variation of symptoms.

(b) *Clinical picture.*—Especially the characteristic dermatitis with glossitis, diarrhœa and mental deterioration.

(c) *Laboratory tests.*—Decreased niacin in the urine and in the blood are the rule but the methods of estimating it are very complicated and certainly not within the scope of an ordinary diagnostic laboratory.

(d) *The therapeutic test.*—This must be interpreted with reserve; all skin conditions are liable to improve by the administration of large doses of niacin but the improvement will not be so dramatic as in pellagra. On

the other hand there are some cases that resist treatment with niacin it should be given both orally and parenterally

The skin condition has to be differentiated from sunburn poison ivy dermatitis, trade dermatitis lupus vulgaris lupus erythemato is erythema multiformis and syphilis the gastro-intestinal symptom from nutritional diarrhoeas and sprue (in these there is usually more commonly a macrocytic anæmia and less commonly achlorhydria and in sprue there is fatty diarrhœa and a flat blood glucose curve on oral administration) and the nervous and mental symptoms from neurasthenia beri beri ergotism lathyrism tabes, Korsakoff's and Wernicke's syndromes and general paralysis of the insane

PREVENTION

As pellagra is a dietetic disease, its prevention is primarily an economic and educational problem rather than a medical one However the distribution of specific preventive substances at the worst period of the year and the provision of early medical relief should form part of any anti pellagra campaign

Maize is only used as a staple diet because the people cannot get anything better and provided it is suitably supplemented its consumption is not detrimental to health the aim should therefore be the encouragement of suitable supplementation rather than the radical alteration of the diet.

Much can be done by education and propaganda It is first necessary to make the people understand the necessity for including certain substances in their diet and many will find the means for doing so if not at first perhaps at least in the course of a few years Again, if they are made familiar with the signs and symptoms of the disease, and are made to understand that it is amenable to treatment and if treatment is put within their reach they will probably present themselves for treatment in the earlier stages of the disease when its progress can be checked easily

Naturally methods of improving the economic status of pellagrous populations must be explored but short of this it may be possible to encourage and even provide the means for home gardening or poultry keeping, and at the worst times of the year to distribute dried yeast or even tablets of niacin (100 mg daily) through schools or other channels

The best supplementary foods are fresh meat, especially pork, liver whole-grain cereals and green leafy vegetables It may be necessary to fall back on tinned (canned) vegetables fish and meat which will serve the same purpose but less effectively The principle should be to increase the proportion of protein as well as to provide an adequate amount of vitamin B_2 complex.

In institutions or camps the disease should never arise if the diet are properly designed but in the case of actual food shortages when it may be necessary to fall back on some poorer staple substances such as maize dried yeast should be provided.

Dried yeast autolysed yeast or marmite (vegex) or some similar preparation is also a useful supplement for restricted invalid diets when for any reason it may be necessary to restrict other pellagra preventing foods

TREATMENT

The treatment of pellagra seldom presents much difficulty in so far as treatment of the individual moderately advanced case is concerned the real difficulty arises in the treatment of large poor population and

here the medical aspects are over-shadowed by the economic ones. Treatment can be considered under the four headings general dietetic specific and *symptomatic*

General.—The patient should be removed from the unsatisfactory conditions under which he is living and *put into hospital or at least to bed under good home-nursing conditions* The room should be light and airy, but direct sunlight should be avoided until the patient's reactions to this have been ascertained. Any concomitant infections such as ankylostomiasis or malaria should be treated, and any other dysfunctions, such as *hypothyroidism and achlorhydria corrected* or compensated

Dietetic.—The patient should be given a good mixed high protein diet, with a calorie value of at least 20 per cent above his normal requirements in which there is fresh meat (including liver, or pork) whole-wheat (or other good cereal) meal leafy vegetables and fresh fruit.

Specific.—In most cases there will be immediate improvement following rest under good hygienic conditions with a good diet, but, if suitable specific treatment is added *the improvement will be more rapid*. The main deficiency in pellagra is the niacin fraction of the vitamin B_2 complex, this must therefore be given first It is best to give large doses—500 mg daily will usually be sufficient—for three or four days and then to follow this up with a maintenance dose of 100 mg daily until all signs and symptoms have disappeared *Niacin can also be given intramuscularly or* intravenously in doses of 100 mg There are no disadvantages in the intramuscular method and it obviates the danger of non absorption, but not more than 10 mg. should be given intravenously by means of a serum syringe, and even this should be given slowly If the larger dose is considered necessary, it should be given in a pint of 5 or 10 per cent glucose slowly Large intravenous doses cause acute peripheral dilatation that may be dangerous. *Niacinamide does not cause this dilatation* and may be given in the full therapeutic doses with impunity

The effect on the skin lesions is immediate and dramatic the writer has seen an excellent case of pellagra entirely spoilt, for teaching purposes, in a period of 48 hours, by an over-enthusiastic house physician ! But *the improvement in the other symptoms may not be so marked* It is very often advisable also to give riboflavin in cases of severe stomatitis, and thiamin in cases complicated with peripheral neuropathy and there are some cases in which liver extract also seems to be necessary suggesting that this contains yet other specific substances. There are some workers who in view of these facts, prefer to treat *all cases of pellagra* with liver extract parenterally and dried yeast by the mouth. Further there are *some* cases in which improvement is only slight and temporary with specific treatment, unless this is combined with a general improvement in the diet and especially with an increase in the intake of good protein

Symptomatic.—Drugs do not form an essential part of the *treatment*, and in uncomplicated cases complete cure can be effected without them but sodium thiosulphate 7 grams daily *will help the skin* condition and arsenic in the form of Fowler's solution is recommended by some writers. The skin will *improve* more rapidly if the area is rubbed with olive oil. If there is a hypochromic anæmia, ferrous sulphate gr vi should be given three times a day

Most of the gastro-intestinal symptoms will disappear on *the administration* of a suitable diet, but, if diarrhœa persists kaolin bismuth or even opium should *be tried in turn and*, if constipation then supervenes, a mild vegetable purgative should be given for a night or two and this should be *followed* by some bowel regulator, such as isapghul every night

The stomatitis, if it does not respond to riboflavin, should be treated with a mild antiseptic, such as borax and glycerine and if it is painful to the extent of interfering with the taking of proper nourishment cocaine may be added to the mouth application two grains to the ounce For the mental symptoms and sleeplessness sedatives such as bromides or luminal may be necessary

PROGNOSIS

This will naturally vary with the circumstances If the patient, even in an advanced stage, can be placed under ideal hygienic and dietetic conditions treatment is usually easy and in most cases will end in complete cure but there may be a relapse when the patient returns to his previous mode of life The disease however usually occurs amongst poor populations where the intensity of the symptoms will vary according to the degree of the dietary deficiency and the usual history is that of improvement during the cold months of the year (in sub-tropical climates) with progressively more severe relapses during the summer months of each year (In India and other tropical countries the disease is active in the cool but sunny winter season and subsides during the hot but cloudy and wet summer)

In a small percentage of cases, the patient appears to resist all forms of treatment and after short temporary remissions deteriorates rapidly and eventually dies of some complication

The death rate in Italy is given as 3 to 5 per cent and in the United States as about 10 per cent, but in some outbreaks in the latter country it has been placed as high as 30 per cent

In alcoholics in chronic malarial and dysenteric subjects and in any febrile state the prognosis is less favourable

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SCURVY*

Definition—Scurvy is a dietary deficiency disease characterized by spongy and bleeding gums and superficial and deep hæmorrhages in different organs and tissues of the body which if unchecked ends fatally. It is caused by the deficiency of vitamin C (ascorbic acid) in the diet, and prevented or cured when it has already developed by the taking of citrus fruits or of other fruits or vegetables containing a sufficiency of this vitamin.

Historical—Scurvy was the first dietary-deficiency disease recognized as such; its cause was known at least three hundred years before the word 'vitamin' was invented. There is little evidence that the disease was known to the early Greek or Indian medical writers and it seems to have made its début in the fifteenth century when long voyages of discovery became fashionable. In 1564 Ronsseus, a Dutch physician, described scurvy and its treatment by means of oranges, but did not suggest that lack of them was the cause of the disease. However from this time onwards the practice of carrying fruit and vegetables, and even growing the latter on ships to prevent scurvy began to be adopted. In 1747 James Lind carried out his classical experiments which showed that the juice of oranges and lemons prevented the development of scurvy and Captain Cook in his voyages of discovery (1772–75) put the principle into practice with most striking results, for he only lost one man from sickness in a voyage of over three years whereas earlier explorers frequently lost 80 per cent of their personnel.

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* The status of scurvy as a tropical disease might well be questioned in view of the fact that several Arctic and Antarctic expeditions have been marred by the occurrence of this disease amongst the personnel; nevertheless the inclusion of a short chapter on this disease can be justified on the ground that whereas the average practitioner in the temperate countries of Europe or America will seldom encounter a case of frank scurvy except possibly in the form of Barlow's disease (infantile scurvy) his opposite number in the tropics may well see a large number of such cases.

The protective substance in citrus fruits was identified by Holst and Frolich in 1912 it was classified as vitamin C (Drummond, 1920) and later given the name ascorbic acid in 1932 it was chemically identified by Szent-Gyorgyi (1933) and independently by Waugh and King and in 1933 it was synthesized by Reichstein Haworth and others

Epidemiology.—Although historically it is a disease of ship board (*vide supra*) ever since the cause of it has been recognized regulations and the shorter duration of voyages have made it a rare condition amongst sailors It still occurs in armies living on canned and dried rations it was rife amongst the British and Indian troops in Iraq during the 1914–18 war It is very liable to occur in Indian, African or Chinese labour forces working in unfamiliar surroundings as the uneducated labourers are often very conservative and do not eat the unfamiliar local fruits and vegetables. It appears to be the most common specific deficiency associated with famines it occurred in India during the Hissar famine in 1940 (Nicol 1940)

Sporadic cases not infrequently occur amongst invalids kept on a milk diet and in the form of Barlow's disease amongst infants fed on boiled or preserved milk or on the milk of stall fed cattle without the supplementation of fruit juice or fresh vegetables.

The disease has no geographical or seasonal limitations and it may occur amongst persons of every race both sexes and all ages. In certain special circumstances it may exhibit a seasonal incidence just as it may appear to attack certain groups in a population but the incidence is always explainable in terms of vitamin C intake

ÆTIOLOGY

Scurvy appears to be a simple vitamin-deficiency disease.

Ascorbic acid which man and other primates and certain other animals notably the guinea pig are unable to synthesize is an essential element for cell metabolism it must therefore be taken in the food or the organism will suffer In health the tissues are saturated with this vitamin so that it takes about six months of deficiency before the signs and symptoms of frank scurvy appear A sub-scurvy state is now recognized evidence of which can sometimes be elicited prior to the onset of frank scurvy

The daily requirements of ascorbic acid are 70 to 100 milligrammes for the adult although 30 milligrammes will prevent the development of scurvy Children require relatively more as also do pregnant and lactating women and persons suffering from fever malaria in particular appears to exhaust the ascorbic acid reserves rapidly

Sources of ascorbic acid.—The classical and probably the most convenient sources of vitamin C are citrus fruits especially oranges and lemons the juice of which contains an average of 60 mg. of ascorbic acid per 100 grammes Other fruits rich in vitamin C are black currant (200 mg.) strawberries (50 mg.) cape gooseberries (50 mg.) pineapples (60 mg.) guavas (300 mg.) papayas (40 mg.) and tomatoes (30 mg.) Fresh leafy vegetables root and tubers also contain large amounts provided that they are fresh and either uncooked or carefully cooked notably spinach cabbage, cauliflower parsley green pea sprouts knol khol celery drumsticks amaranth and coriander and potatoes sweet potatoes turnips and beetroot. A very rich source of vitamin C in India is *amla* (*Phyllanthus emblica*) which grows in many forests it contains when fresh as much as 600 mg. per 100 grammes Powdered *amla* maintains about 50 per cent of its vitamin C in an active state

Ascorbic acid is very labile and is very likely to be destroyed by cooking and canning It is preserved best in an acid medium so that the addition of sodium bicarbonate to vegetables during cooking is a bad

practice It is destroyed by *prolonged cooking* and is water soluble so that much is lost if the cooking water is discarded Copper cooking vessels will cause excessive destruction of ascorbic acid. In many brands of canned fruit, *less than 30 per cent of the original content* of ascorbic acid is preserved but modern canning methods preserve much more than this. Again, during storage of potatoes for example the ascorbic acid is quickly lost.

Milk is not a good source of ascorbic acid, but if the cow is fed on fresh grass, its milk will contain far more than if it is stall fed Most pasteurized milk supplied in cities is a negligible source of vitamin C *Human milk is a much better source than cow's milk.*

When fresh fruit and vegetables are hard to obtain ascorbic acid can be supplied by sprouting pulses or cereals, unmilled grain is of course necessary The following method of preparing sprouted grain is given by Aykroyd (1941) —

'Dāl, gram, wheat, unsplit peas or any other grain is first soaked in water for 24 hours and is then spread out on damp earth or on a damp blanket and covered over with a moist cloth or sack (gunny bag) which is kept moist by sprinkling water upon it from time to time. After two or three days the grains will have sprouted and be ready for use

'The sprouted grains should be eaten raw or after cooking for not more than 10 minutes

PATHOLOGY

The deficiency of vitamin C causes an imperfect formation of connective tissue with failure to develop true supporting tissue there is no proper adhesion between the cells of the epithelium of the capillary walls so that these rupture very easily on the slightest trauma or when the internal pressure is increased and similarly scar tissue does not form properly and is very weak. Osteoblasts fail to differentiate, and there is deficient formation of calcified osseous matrix so that eventually the osteoblasts come to lie in an almost exclusively fibrous matrix, and further development ceases It has been reported that in advanced cases large areas of erythroblastic and leucoblastic bone-marrow tissues are replaced by 'amyloid' connective tissue

The post-mortem picture will be largely influenced by the secondary deficiencies and the superimposed infections but a constant finding will be numerous hæmorrhages in most of the tissues and organs including the brain.

Blood picture—A microcytic hypochromic anæmia that responds readily to the administration of vitamin C has been reported, but the writer has never been able to identify any anæmia as due to ascorbic acid deficiency and recent experimental work has failed to establish the earlier claims.

SYMPTOMATOLOGY

Latent period—In infants 'Barlow's disease' usually *develops between* the sixth and the eighteenth month, and similarly in a well saturated adult, it is about six months before there is any clinical evidence of the deficiency although in a case in which a partial deficiency has existed *for some time* the disease may be precipitated within a shorter period.

Onset.—The first signs are pallor breathlessness anorexia and general weakness this is followed by sponginess and bleeding of the gums then swelling so that they almost envelop the teeth which become loose and may fall out at the same time petechial hæmorrhages occur in the skin and there may be deep hæmorrhages in the muscles which are *evidenced* by the sudden appearance of tender swellings

Progress.—Large ecchymoses may appear in the skin then sub-periosteal hæmorrhages, and there may be hæmorrhages into the joints and other serous cavities or even into the brain There may be hæmoptysis hæmatemesis hæmaturia and/or melæna Meanwhile severe anæmia may be developing this is partly due to the loss of blood but also it is claimed, to the bone-marrow changes The gums become secondarily infected so that there is a foul gingivitis and the teeth drop out and usually the patient becomes progressively weaker and eventually dies of some complication such as pneumonia

In infants the most striking additional feature is the extreme tenderness of the joints so that the infant is terrified when anyone approaches its cot. If the knee is flexed and everted a swelling of the lower end of the femur will be seen which is usually symmetrical this is not tender Later the upper limbs may be similarly affected There is also usually radiological evidence e g sub-epiphyseal hæmorrhage or cessation of the development The spongy gums and other signs will also be present

Diagnosis.—This can be made on (a) the dietetic history (b) the clinical examination (c) the therapeutic test and/or (d) certain clinical and laboratory tests.

Frank scurvy will usually present little difficulty from a clinical point of view if there is a dietary history that is compatible with vitamin-C deficiency However it is unwise to diagnose scurvy in an adult on a mixed diet or in a breast fed child on clinical examination alone in such cases the confirmation of the diagnosis by laboratory tests or at least the therapeutic test, should be awaited. A good clinical response within a few days to a daily dose of 700 mg of ascorbic acid constitutes a positive therapeutic test the converse may also be accepted

A relatively simple clinical test is Gothlin s capillary fragility test: a sphygmomanometer band is placed on the arm and the pressure raised to 90 mm. of mercury for three minutes the arm below the bend is then inspected with a hand lens and in cases of deficiency there will be numerous capillary hæmorrhages. No clinical test is however entirely reliable although this i better than Rotter s intradermal test which most reliable workers have now discarded

Of the laboratory tests the estimation of the urinary excretion of ascorbic acid is the simplest. On a minimum adequate intake of 25 mg the daily excretion is about 18 mg there is a sharp response to a test dose of 700 mg if the subject is saturated but if not it may be several days before there is evidence of an overflow in the urine. The urinary ascorbic acid falls to *nil* in frank scurvy and no appreciable amount i excreted until at least one gramme of ascorbic acid has been given

The estimation of the blood ascorbic acid is also relatively simple If thi i as high a 0 7 milligramme per 100 c cm it may be assumed that the patient is saturated. A low value does not however necessarily mean that there i ascorbic acid deficiency

In differential diagnosis most of the hæmorrhagic diseases will have to be considered and it may be necessary to make a platelet count and to do a prothrombin test

PREVENTION

The prevention of scurvy has been practised on ships of the navie and merchant services of many nations for several hundred years often by regulations that make it compulsory to carry fresh fruit or fruit juic for consumption by the crew In institutions and armies it can be prevented by including in the ration some good source of vitamin C and by training cooks not to destroy such of the vitamin a is present in raw

food by over cooking it or by using copper or brass utensils. When all other sources are precluded, it can be provided by sprouting grain (*vide supra*)

The present shortage of shipping has reduced the amount of the citrus fruit that can be imported into Great Britain To replace this deficiency, synthetic vitamin C is being used freely

Education and propaganda play an important part in prevention the importance of taking fresh fruit and vegetables or sprouted grain, should be impressed on school children and pregnant women in particular, the latter for their own benefit and for that of their infants.

As a general rule the prevention of scurvy is not so much an economic problem as is the prevention of pellagra or even beri beri, but this aspect will arise in the case of famines. During the Hissar famine in 1940, powdered *amla* was distributed and did much to reduce the incidence of scurvy *Amla* powder is also being issued to troops based on India and it is hoped that this will obviate any recurrence during this war of the scurvy that was a serious source of illness in Iraq in the last war

Infants on artificial food or on pasteurised milk should always be given fresh fruit juice daily, this will also apply to infants whose mothers are on a low ascorbic acid intake and in fact, it will be a safe precaution to apply to all infants as well as to invalids on milk diet.

TREATMENT

This presents no difficulties if fruit juice or synthetic ascorbic acid is available Doses up to 700 mg of *l*-ascorbic acid should be given by mouth daily for the first few days until the acute symptoms subside. In very acute cases it may be safer to give 500 mg. parenterally A maintenance dose of 100 to 200 mg. should be continued for a few weeks until it is certain that saturation is complete, which of course could be ascertained by the estimation of the urinary secretion of ascorbic acid, but this is not usually necessary Infants require 40 mg. daily for two or three weeks. When synthetic ascorbic acid is used, it is good practice to supply a natural source of vitamin C in the diet as well since cases have been reported in which the response to the synthetic vitamin alone was not satisfactory

Subsidiary treatment is seldom necessary but the correction of this deficiency may uncover other deficiencies so that a diet rich in all important vitamins should be given whenever possible.

If the specific treatment is given even in advanced cases, the prognosis is usually good.

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EPIDEMIC DROPSY*

Definition.—Epidemic dropsy is the provisional (and not very appropriate) name given to a non-infectious disease which is characterized by gastro-intestinal disturbances, œdema of the extremities, certain specific skin manifestations and cardiac dysfunction, and is frequently fatal. It has a very limited geographical and racial distribution, being confined mainly to Bengal and Bengalis, and its exact ætiology is as yet unknown, but it is undoubtedly associated with food and probably with mustard oil.

Discussion.—This disease has in the past suffered many things of many theorists. It has been fitted into a variety of categories to which it quite obviously does not belong by both local and long-distance investigators, who have exalted casual clinical observations of secondary importance—both in this disease and in the diseases to which they have attempted to liken it—to the position of main symptoms and have then

* The clinical paragraphs of this paper were written with the aid of some notes given to the writer for this purpose by Dr R. N. Chaudhuri, his late colleague and the officiating professor of tropical medicine in Calcutta, whose clinical experience of this disease antedates the writer's by several years.

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may be misleading Very few investigations of this nature have been undertaken, but it is only through such investigations that we are likely to reach a solution of the problems

Recent work.—An epidemiological investigation was undertaken by Dr R. B Lal the professor of epidemiology and vital statistics at the All India Institute of Hygiene Calcutta, and his staff, in six different areas in Bengal, Bihar and Assam including a tea estate where an outbreak of the disease had been recognized and reported by Dr Charles Terrell. These investigations appear to point once more to mustard oil as the probable vehicle of the noxious factor and the same workers, in an investigation conducted with the clinical collaboration of members of the staff of the Calcutta School of Tropical Medicine, were able to produce suggestive symptoms in volunteers fed on samples of mustard oil that has come under suspicion in epidemic dropsy outbreaks (Lal *et al.* 1937–41)

During the last half century, mustard oil has been suspected repeatedly but in 1926 Sarkar recorded an outbreak in which several patients had all the symptoms of severe epidemic dropsy after taking oil that had been contaminated with argemone oil (from the seed of *Argemone mexicana* local names *salkata* or *katakar* oil) In 1928 Kamath, reporting an outbreak in which mustard oil was taken, and applying his data to support the infection theory noted that oil from a seed, known locally as *odusman*, was also used this seed has now been identified as *Argemone mexicana*.

Attention was thus directed to a specific contaminant of mustard oil and feeding experiments were carried out at the Calcutta School of Tropical Medicine on human volunteers and on animals (Chopra *et al* 1939), with very suggestive results.

We have now arrived at the position in which mustard oil has been incriminated once more, but on this occasion the case against it rests on a much sounder basis of epidemiological and experimental evidence. Argemone oil a common adulterant of mustard oil has been shown to produce symptoms identical with those of epidemic dropsy, whether it is administered accidentally or experimentally Finally in a number of recent outbreaks, it has been found that the mustard oil used by the victims was badly contaminated with argemone oil, and that when its use was discontinued the outbreak subsided.

We know that argemone oil contains a noxious agent, but up to the present time chemists and pharmacologists are not agreed as to its exact nature or how it acts whether it is an independent poison that produces its ill effects grain for grain according to the dose in which it is taken or whether the substratum is an important factor and the degree of toxicity depends on the excess of one food substance in the diet or on the absence of another

Argemone oil is not an adulterant in the sense that it is often added to the oil by the retailer deliberately for the sake of increasing his profit but it is an accidental contaminant of the mustard crop as it grows in the field it is a self-sown weed which can be distinguished easily from the mustard plant when the crop is harvested, and although the seeds are very similar they could be picked out by a careful farmer

It is quite understandable that some years would be more favourable to the weed than others and that its percentage incidence in the crop will vary from place to place but apparently it is a very common contaminant and a large number of samples of oil show its presence, so that it is easier to account for the wide prevalence of the disease than it is to understand why it is not more prevalent. It is for example, not quite clear why epidemic dropsy is comparatively rare amongst the

poorer Anglo-Indian community who use mustard oil for cooking almost exclusively Does it depend on the amount of argemone oil present? Lal and his co-workers (1941) place the maximum safe amount at 0 5 per cent Is it simply because it is heated and partly inactivated or is it something to do with the general composition of their diet in which rice does not preponderate to the extent that it does in most Bengali diets?

There has long been a strong belief prevalent amongst both patients and doctors, that rice *per se* is bad for an epidemic dropsy patient this belief is independent of the rice toxin theory because it applies to any form of rice, sound or diseased Dr Ellis C Wilson studying cases in the hospital of the Calcutta School of Tropical Medicine, noted that there was a distinct increase in the œdema whenever an epidemic dropsy patient was given a rice diet. There is therefore some evidence that people who live on a diet consisting largely of rice possibly by virtue of its high carbohydrate/vitamin B ratio are more susceptible to the disease and that rice though not the main culprit or the vehicle of the noxious factor does play a part in the ætiology of epidemic dropsy

In the study of vitamins the idea of conditioned toxicity is now gaining ground there are numerous examples reported of the toxic effect of a toxic substance being conditioned by the nature of the diet, and/or the state of vitamin saturation of the subject *e.g* selenium poisoning and a high protein diet, lead poisoning and vitamin C and indol and vitamin B Is this possibly another such example? Such an hypothesis would provide a means of co-ordinating some of the earlier theories regarding epidemic dropsy with the latest one for specific food deficiency was visualized as a possible cause long before the present vitamin age

Both the clinical and the pathological evidence (*vide infra*) support the epidemiological and experimental evidence and indicate that the disease is far more likely to be due to an intoxication than to either an infection or a vitamin or other food deficiency

To summarize epidemic dropsy is apparently caused by the consumption of some toxic substance in mustard oil, probably a constituent of argemone oil a common contaminant of mustard oil the effect of this toxin is enhanced if the diet is predominantly a rice one

PATHOLOGY

The characteristic pathological change is a persistent dilatation of the smaller blood vessels not simply of the capillaries in all the layers of the skin in the heart muscle and in other organs and tissues associated with slight perivascular infiltration by large mononuclear cells increased permeability and local œdema The toxin appears to have a direct specific action on small blood vessels

These changes can be seen in all the layers of the skin and in the sub papillary plexus there is often new vascular formation which may progress to the development of a hæmangiomatous condition that gives rise to the so-called "sarcoids There is often increased pigmentation in the basal layer and some pigment will be seen in the deeper layers of the skin There is œdema in the corium where the collagen fibres may be swollen and in the subcutaneous tissue The sarcoid is a vascular tumour with a few connective tissue cells no fibroblasts and no inflammatory cell exudate covered by a flattened epidermis which shows thickening and down growth deep into the normal corium at the edge of the tumour

In the heart, there is marked vascular dilatation between the muscle fibres so much so that sections sometimes give the appearance of free

extravasations of blood that have dissected out individual muscle fibres or bunches of fibres

In the eyes there is great engorgement of the uvea which results in over production of aqueous humour increased tension in the anterior chamber, and glaucoma

The blood picture—There is usually a distinct normocytic orthochromic anæmia which is apparently due to depressed hæmopoietic function (Sen Gupta and Napier, 1940) The leucocyte count is usually slightly raised and there is a shift to the left in Arneth count The erythrocyte sedimentation rate is increased considerably

The urine shows no constant changes there is however frequently a trace of albumin

SYMPTOMATOLOGY

The *latent period* between the consumption of the noxious material and the onset of the first symptoms (this can sometimes be estimated with a fair degree of certainty but of course at other times not) is very variable, from two or three days to two or three weeks. It is probably dependent on the dose taken. Similarly the onset may be sudden, or insidious again, this probably depends on the same circumstances. It is usually possible to obtain a history of nausea loss of appetite, and looseness of the bowels for a few days with this there may have been irregular fever but there is seldom much fever by the time the patient reaches the hospital, though the diarrhœa often persists.

In the acute cases breathlessness on the slightest exertion, swelling of the feet, which is much worse towards the end of the day and, in some outbreaks, skin manifestations will develop rapidly The pulse rate is usually rapid and may be very irregular the blood pressure is variable In very severe cases, the heart condition progresses rapidly and the patient, now confined to bed is orthopnœic, or he may die suddenly before the full seriousness is appreciated In the less severe cases œdema and shortness of breath will persist as long as he is working and taking a rice diet but will subside rapidly under the hospital treatment and the hyperæmia of the skin may subside leaving the sarcoids.

Finally, all the more acute manifestations subside, and, as long as the patient remains in bed he feels perfectly well but he may be left with a weakened myocardium which prevents him from returning to full work for many months There are, however, amongst better-class patients, many whose cardiac condition appears to be normal but in whom a cardiac neurosis develops that is even harder to cure than any true cardiac dysfunction.

Some of the symptoms will be considered in a little more detail.

The œdema, which is both central and peripheral in origin, is an almost constant symptom but variable in degree and very rarely general anasarca develops.

The cutaneous manifestations are very common in some outbreaks and apparently rare in others. In 1934, out of 39 cases admitted to the School of Tropical Medicine 16 showed some cutaneous lesion and, since special attention has been drawn to them, they appear to be more common than they were hitherto They include a generalized purplish erythema, vascular mottling of the skin, hyperpigmentation of the exposed parts particularly the face a petechial rash, and the so-called *sarcoids*.

The sarcoid (quite unrelated either ætiologically or histologically to Boeck's benign sarcoid and equally as unlike a sarcoma although admittedly a fleshy tumour) is a hæmangiomatous growth, it varies from the size of a pin's head to that of a walnut and it may be sessile or

pedunculated It is easily injured and is liable to bleed freely and more rarely to suppurate

The heart—This is frequently enlarged. A mitral systolic murmur due to relative mitral incompetence and an accentuated pulmonary second sound due to congestion of the lungs are common and there may be a pulmonary systolic murmur due to dilatation of the pulmonary artery In severe cases there are signs of congestive cardiac failure

The electrocardiogram commonly shows functional derangement tachycardia of sinus origin and extra-systoles are not infrequent the P R interval has been found to be abnormally short in a large percentage of the cases investigated and an abnormal T wave and auricular fibrillation have been found Orthodiagrams frequently show that the heart is enlarged especially the left ventricle and the right auricle

Other symptoms—Patients often complain of burning or a pricking sensation and of vague pains all over the body but very rarely of definite neuritic paralyses or areas of anæsthesia The knee jerks sometimes appear to be brisk at first and later poor or even lost but in most cases there is little deviation from normal in any reflex. (Some of these symptoms may of course be due to associated thiamin deficiency)

Glaucoma develops in about five per cent of cases There is early complaint of rainbow haloes around a light dimness of vision then progressive contraction of the visual field and if unrelieved eventually complete blindness There is usually little pain but on examination the increase in tension will be obvious

Abortion is the rule in pregnant women

DIAGNOSIS

This is based on the clinical picture and the dietetic history If several members of a family give a history of acute diarrhœa followed by œdema of the legs with or without flushing which is warm to the touch, and shortness of breath on exertion careful enquiries should be made regarding the diet of the family and other members should be examined and questioned for minor signs of the disease

The characteristic œdema and erythema is not matched in any other condition nor are the so-called sarcoids though these are somewhat like the eruption in verruga peruviana (another local disease that occurs curiously enough on almost exactly the opposite side of the globe) The disease has to be distinguished from several other conditions in which there is swelling of the legs *e.g* filariasis ankylostomiasis schistosomiasis and cardiovascular and renal disease but the one that calls for comment here in view of a persistent misconception on the subject is beri beri Between epidemic dropsy and the dry form of beri beri, with its gradual onset wasting and weakness and *pronounced* neuropathies there are no points of similarity to be discussed. In the wet form, the latent period is again longer than that of epidemic dropsy the œdema often disguises underlying wasting and neuropathies, and is cold that is unaccompanied by hyperæmia there are no other cutaneous manifestations and in the heart condition there is very frequently a dramatic response to the administration of thiamin chloride All these points taken together will usually make it easy to distinguish even isolated cases and when there is a group of cases should make confusion impossible

PREVENTION

It is obvious that this will depend on the final verdict on the cause of the disease but the present state of our knowledge certainly justifies

the adoption of public health measures aimed at the prevention of the contamination of mustard oil by argemone oil, even as an experimental measure.

Preventive measures must be started with the agriculturist to whom the danger of allowing his crop to be contaminated by this dangerous weed should be pointed out It may however be easier to bring pressure to bear on him indirectly by inspecting the seed that is sent to the oil press and condemning all batches that contain more than a certain percentage of seeds of *Argemone mexicana* or even by testing the oil that is supplied to the retailer But there are technical difficulties about the latter procedure, as the nitric acid test,* which has up to now been relied upon for detecting contamination is not entirely specific

An interesting observation was made by Terrell (personal communication) namely that in some northerly districts of Assam the mustard and the *Argemone mexicana* do not ripen coincidentally so that the latter seed is not harvested in these districts the mustard oil is never contaminated and epidemic dropsy does not occur

As far as the individual is concerned the only advice one can give is to warn him to buy his oil from a safe source and/or to have it tested.

TREATMENT

This is essentially symptomatic and dietetic no specific is known

Rest is the first essential even if the cardiac symptoms are not prominent, as until the patient has been placed on his new dietary regime for several days they may at any time supervene If cardiac symptoms have already developed he must be kept in bed and carefully nursed until they have completely disappeared and after graded exercise have shown no sign of returning

The diet will depend on the symptoms to some extent but if there are no contra indications a well balanced diet containing at least the full quota of protein and from which rice and mustard oil are excluded, should be given Bread or *chappatis* should be given in the place of rice. If the diarrhœa persists this may be stopped by placing the patient on milk or even lime whey and albumin water may be necessary for a few days but care must be taken not to keep up this restricted dietary for too long, and if there is much œdema so much fluid may be contra indicated. In the latter case, salt also should be restricted

Drugs.—An initial purgation with two drachms of liquorice powder at night followed by two or three days of administration of castor-oil emulsion (a drachm to the ounce) or one drachm of sodium sulphate every two hours for the first day and every four hours for the next two days will help to control the diarrhœa and to some extent the œdema but, if after this the former persists bismuth and opium should be substituted.

A mixture containing tincture of ephedra 20 to 30 minims and 10 to 15 grains of calcium lactate, thrice daily, is prescribed as a routine procedure at the Calcutta School of Tropical Medicine, theoretically because ephedrine is vasoconstrictor and a circulatory stimulant at least, patients appear to do well on it A diuretic *e g* diuretin grs 10 is added if there is any œdema If the œdema is more extensive ammonium chloride grs 10 is given three times a day and then an injection of one of the mercurial diuretics such as neptal or mersalyl. For congestive heart

* About 10 c.cm of the oil is shaken up with an equal quantity of colourless nitric acid after two minutes a *yellow or reddish-brown layer* appears at the bottom of the test tube The test is reported to be roughly quantitative and to detect about 1 per cent of argemone oil

failure digitalis in adequate doses should be given and in severe cases venesection may be advisable

Complications must be treated as they arise the fluid may have to be removed from serous cavities Glaucoma must be watched carefully, and if there i no improvement with general treatment and the visual fields tend to diminish trephining or anterior sclerotomy may be necessary

PROGNOSIS

Even in the mild case the patient is not really fit for manual work within three to four weeks in the moderately severe case with any evidence of cardiac involvement, he will not be fit to resume even clerical work within this period and in the severe case the patient will be incapacitated for several months

The death rate in an outbreak will usually be about 5 per cent, but in some severely affected families half the members have died. Death i from heart failure

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C

INFANTILE CIRRHOSIS OF THE LIVER

by

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Introduction.—In private practice more than in hospital practice, in eastern and southern India, it is not uncommon to encounter children with a definite enlargement of the liver for which no obvious cause is found. The enlargement is progressive and painless and is often associated with irregular fever and digestive disturbances If the condition is not treated early or if it fails to respond to treatment clinical evidence of cirrhosis of the liver soon appears and the child invariably dies

EPIDEMIOLOGY

Incidence.—Hospital reports in India do not usually reflect the true state of affairs as parents will not bring their children to hospital. In a series of 1 100 children investigated by Rao (1934) in Vizagapatam enlargement of the liver was found in 158 cases of which 28 (or 2.5 per cent) were due to cirrhosis Manson Bahr (1940) gives the figure 1 748 for the number of deaths in Calcutta between 1891 and 1893 and recent Calcutta Corporation reports give an average of a little over 300 deaths a year It is more common in urban than in rural populations

Geographical distribution.—The disease is particularly common on the eastern side of India in Bengal Madras and Mysore but cases are reported from Bihar Orissa and the Central and United Provinces It is not seen in hill stations

Age, sex, race, and social status.—Children between the ages of six months and two years (the dentition period) are most commonly affected, but the disease is sometimes seen in older children

Children of both sexes are affected but possibly there is a slight male predominance. It is popularly said that the first male child after a series of females is likely to be affected the explanation might be that it

is the most pampered child who will be likely to have artificial and unsuitable food pressed upon it.

The disease has a remarkable predilection for the Hindu community and is most common amongst orthodox Hindus who are strict vegetarians. In the series of 1 748 cases referred to above 1 616 were in Hindus and *Narayanamurthi and Tirumurti (1939) reported a series of 445 cases none* of which was in either Mohammedans or Anglo-Indians

The vast majority of the children come from middle-class families

Heredity—There is a strong indication of an hereditary tendency, it is usual for several children in the same family to suffer as each reaches the crucial age

ÆTIOLOGY

This is obscure Inherited predisposition and defective feeding are the most important factors Early marriage repeated childbirths and an ill balanced dietary affect both the mother s and the child s health. The mother is unable to nurse the child properly and artificial feeding is started early This is usually badly done, rice sweets fats (buffalo milk) are given the vitamins are not considered and the protein intake is low The child suffers from gastro-intestinal upsets and the toxins that are absorbed are not properly dealt with by the liver Presumably an inborn error renders the liver cells peculiarly vulnerable to toxin and they undergo degenerative changes

PATHOLOGY

As a result of the toxic action the liver cells become necrosed and absorbed. The healthy cells multiply to replace the loss and there is also a secondary fibrotic change commencing in the centre of the lobule *The fibrous tissue develops within the lobule between the cells* (inter cellular cirrhosis) With the regeneration of the liver cells there is also formation of new biliary channels In the advanced stage portal cirrhosis supervenes, with the resultant ascites and jaundice

Blood picture.—There is a very distinct microcytic anæmia, and a pronounced leucocytosis The latter is usually between 15 and 20 thousand per c.mm but the normal proportions of the differential count are main tained.

SYMPTOMATOLOGY

The onset is insidious During the prodromal stage the child although appearing well nourished, becomes peevish irritable and refuses food. He is constipated the stools are pale and pasty or muddy There is flatulent distension of the abdomen. The child does not sleep well and has periods of low fever

The symptoms may be absent or may be overlooked, until the liver becomes large The liver enlarges progressively it is firm to the touch the margin is sharp and it is not tender The spleen is often slightly enlarged The earlier signs and symptoms become more developed and the child begins to lose weight progressively and the skin looks pale dusky and icteric

Later the liver becomes harder and contracts jaundice and the con stitutional symptoms increase and there may be high irregular fever Gradually all the signs of portal obstruction become manifest ascites develops and the child dies of cholæmia or of some complication such as broncho-pneumonia

The course of the disease is variable but on the average it lasts about 18 months and unless early treatment is instituted it is always fatal

DIAGNOSIS

Early diagnosis is important if the child's life is to be saved Peevishness irritability and loss of weight in a child whose liver appears to be painlessly enlarging should be viewed with suspicion particularly if there is a family history of children dying of similar illness between the ages of 6 months and three years A leucocytosis will add to the suspicion.

Other forms of liver enlargement must be excluded amoebic hepatitis or abscess cause pain and tenderness and is uncommon in a young child the absence of parasites, the leucocytosis and a negative aldehyde test will exclude malaria and kala azar leukaemia and van Jaksch's disease will be excluded by the blood count Hodgkin's disease by the absence of enlarged glands rickets by the absence of the bony changes and congenital syphilis by the absence of stigmata and by a negative Wassermann reaction.

Prevention—The measures consist of —

(a) If one or more children in a family have had the disease and perhaps died, an expectant mother with any young children may be advised to leave the endemic area

(b) Spacing pregnancies and general attention to the health of the prospective mother

(c) Ante- and post-natal care

(d) Attention to the infant's diet continuance of breast feeding with suitable additions to the diet, especially vitamins a properly designed dietary regime if artificial feeding has to be resorted to and careful avoidance of excess of fat and carbohydrates.

Treatment—Diet is the most important part of the treatment. Excess of fat being detrimental to the liver function this element should be omitted or cut down to the minimum Carbohydrates are given in an easily assimilated form. Restriction of protein is not only unnecessary but actually harmful Extra protein is given in the form of white of egg casein, *dal and later fish and chicken if religious considerations allow it* Vitamin concentrates, particularly of the B group in the form of yeast should be given The fat reduction makes the addition of A and D advisable Skimmed milk glucose and fruit juice should form the basis of the diet as the condition improves, whole milk can be added slowly

Drugs.—Grey powder with Gregory's powder and sodium bicarbonate given two or three times a day in suitable doses for the first 10 to 15 days will usually improve the bowel condition A vegetable cholagogue *e g* liquid kalmeg may be given in doses of 20 to 30 drops in water or a bile preparation.

Otherwise, treatment is symptomatic iron may be required for the *anaemia and diuretics with paracentesis* if indicated for the ascites Intercurrent infections such as ascaris should be suitably treated

A change to a non-endemic area especially a hill climate may be advisable *for earlier cases*

PROGNOSIS

If rigid dietetic treatment is instituted early the life of the child may be saved. If however signs of portal cirrhosis ascites and jaundice appear the outlook is usually hopeless

The earlier *the age at which the signs appear* the worse the prognosis and a history of the disease in the family is a bad prognostic portent.

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LATHYRISM

Definition —Lathyrism is a syndrome of which the most prominent clinical feature is muscular weakness and later spastic paraplegia it occurs especially during times of drought and famine amongst certain population groups whose staple diet is a vetch *Lathyrus* in India Spain and elsewhere.

Historical —The condition wa recognized as a dietetic disease by the early Indian medical writers and later by Hippocrates. In the 17th century it was definitely associated with the eating of the vetch *Lathyrus* from which it derived its nam and in some European countries edicts were proclaimed forbidding its use. In India the condition w reported early in the last century by several British physicians and since then outbreak ha e occurred frequently

EPIDEMIOLOGY

The disease has appeared in several European continental countries including France Italy and Spain (in Barcelona Cuenca Ciudad Real Toledo Valladolid and Madrid provinces) in North Africa Abyssinia Iran and in India (the Central and United Provinces Central Indian States and Bihar in particular) In North Rewah (Central India) in 1921 it was estimated that 6 per cent of the total population of about a million people were affected There have been a number of recent report of the condition in Spain (Jimenez Diaz *et al* 1943 and Martinez Almeida 1943)

The persons most affected are males between the ages of 15 and 30 that is during the most active period of their lives

It i a disease of famine years and it occurs almost exclusively amongst members of the lowest economic cla es but the individuals affected are often well nouri hed since the vetch provide a diet of high calorie value

ÆTIOLOGY

The actual cause of the disease is still in doubt. It is not a pure deficiency disease as the clinical and pathological pictures do not coincide with any of the known deficiency states and it is confined to certain areas and exclu vely to person living on one particular staple diet namely the

vetch *Lathyrus* In India *Lathyrus sativa*, locally known as *khesari dál*, is incriminated but in other countries *L cicera* and *L clymenum* are the common vetches used

On the other hand it is almost certainly not a pure food intoxication, for the vetch is used by many people as a staple diet and by a much wider group as an additional item in the diet without causing any of the symptoms of lathyrism

There seem to be three possibilities —

(*a*) That it is caused by toxins derived from *Lathyrus sativa* which has been grown under certain special conditions or which has undergone certain changes after harvesting, through having been kept in damp storage for example

(*b*) That it is due to contamination of the *Lathyrus* crop by some other vetch, *e g* *Vicia sativa* locally known as *akta*, that is not easily distinguished from *Lathyrus sativa* and which either normally or under special circumstances is toxic

(*c*) That the disease is a conditioned toxicity, that is to say the pathological changes are caused by a toxin in *Lathyrus* or less probably in some common contaminant of the *Lathyrus* crop, in the absence of some vitamin or other food factor that normally neutralizes its effect. This has for some time been the present writer's interpretation of some of the apparently contradictory observations regarding the ætiology of this disease in India the recent work of Jiménez Díaz and others (1943) in Spain seems to provide considerable support for this hypothesis

Toxins were isolated from the germinating *Lathyrus sativa* by Acton and Chopra (1922) and from *Vicia sativa* var *angustifolia*, Anderson, Howard and Simonsen (1925) have isolated a toxic base divicine which has the properties of an alkaloid and which will cause changes in the central nervous system in experimental animals. In India the epidemiological and experimental evidence incriminating, on the one hand *Lathyrus sativa* and on the other the contaminating vetch is in both cases contradictory

By feeding monkeys on pure samples of lathyrus peas Stockman (1929) in Glasgow produced a temporary spastic paralysis that was very similar to the more permanent condition lathyrism observed in man. Geiger Steenbock and Parsons (1933) produced lameness, spinal curvature and bone changes in rats by feeding them to the extent of 25 per cent and 50 per cent of their diet, on the seeds of *Lathyrus odoratus* the sweet-pea in the latter experiments, the higher the percentage of the peas, the greater the disability which was not prevented but reduced in degree by the giving of cod-liver oil coincidentally

Lewis and Esterer (1943) produced a similar condition in rats by the cold-water extract of the sweet-pea the rats were not protected by the addition of vitamin C to their diet

Jiménez Díaz and co-workers (1943) have concluded that the condition is due to eating large quantities of the vetch *Lathyrus* to the exclusion of other dietary substances, that the actual toxin is associated with the lipoid fraction, and that there exists a water-soluble thermostable substance that if taken in sufficient amount will antagonize the vetch toxin. *This antagonistic substance* is not a vitamin and can apparently be synthesized by some animals (but not by man or the horse) and is present in most food of animal origin

The horse is apparently the only other mammal commonly *affected* in nature.

PATHOLOGY

Degenerative changes have been reported in the crossed and direct pyramidal tracts and in the *column of Goll* The cell content of the cerebrospinal fluid is normal but an increase of protein has been reported

SYMPTOMATOLOGY

The condition appears *usually after* the patient has been on the incriminated diet *for two or more months* Prodromal symptoms consisting of numbness tingling or formication occasionally occur The onset

is usually very sudden and may be associated with fever and chills or it may follow exhaustion and exposure. It seems questionable whether the fever which has been reported in certain cases is part of the syndrome or whether it is the precipitating factor. The common history is that after a period of rest following a day's work or after a more prolonged period in bed as a result of illness the patient finds that he is unable to rise or that his muscles are so weak and tremulous that he can walk only with difficulty. The maximum disability is usually reached within a few days; the fever and constitutional symptoms may subside but there is seldom any regression in the nervous and muscular involvement which is usually permanent.

The fully-developed clinical picture is that of a spastic paraplegia. The knee and ankle jerks are exaggerated and there is ankle clonus and extensor plantar response. The feet are extended, the knees flexed and the legs adducted in varying degrees. The muscles of the lower limbs may become wasted through disuse. The upper limbs usually escape entirely and in fact often show good development on account of the extra work thrown on to them. The sensation and the sphincters are usually unaffected but the sexual powers may be enfeebled.

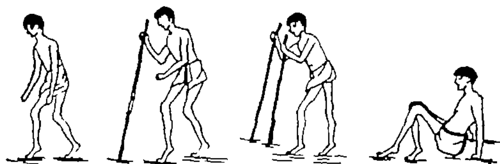


Figure 173

The gait is characteristic. The degree of disability depends on the extent of the damage. The four grades shown in figure 173 are recognized. In the first grade of disability the patient walks stiffly on the balls of his toes tilting the pelvis to raise the feet from the ground. In the second grade, in order to compensate for complete absence of active flexion he has to tilt his pelvis so much that it is difficult to maintain balance without a stick. In the third grade the adduction is so marked that each circumduction of the leg ends in a scissor leg position which necessitates the even support of two sticks to keep the patient erect. In the last grade the patient is unable to walk upright but progresses in a sitting posture by taking the body weight in the hands and balls of the feet and shuffling the buttock forward.

PREVENTION AND TREATMENT

All measures to discourage the use of *Lathyrus* as a staple diet should be taken. These will amount to anti-famine measures by irrigation schemes and by a better distribution of other staple foods during periods of drought, for example. Much has been achieved on these lines in recent years in India. When the toxic substance and/or the hypothetical antagonistic substance have been identified it will probably be possible to take more specific measures, but it has been shown that a high protein diet largely of animal origin will usually arrest, though not reverse, the

pathogenic processes There is little evidence that any impr
be obtained by treatment, when paresis has developed

PROGNOSIS

The vital functions are not involved and the expectation
directly affected but the patients who are mostly of the unec
cultural class become dependent on charity for their subsist

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ANÆMIA IN THE TROPICS

Introduction.—It seems desirable that this subject should be given a separate chapter if for no other reason than to emphasize the facts that in the tropics as in temperate climates anæmia is a symptom and not a disease, that with the possible exception of fever it is the most common symptom of diseases particularly associated with tropical conditions but that there is little evidence that the tropical climate *per se* is ever directly responsible for anæmia in the human subject living on an adequate diet.

Surprisingly little attention was paid to this subject prior to the hæmatological renaissance of the third decade of the present century, a revival of interest that was initiated by the introduction of liver in the treatment of pernicious anæmia. Previous to this it was generally assumed

that the hæmoglobin level of both the natives of, and of the sojourner or settler in tropical countries was much below that of residents in temperate climates it was vaguely assumed that this was due to the depressing effects of heat' but no attempt was made to measure the extent of this 'tropical anæmia nor even to confirm its existence When in 1932 the present writer was asked to investigate for the Indian Tea Association the causes of gross anæmia amongst certain groups of tea-estate labourers, he failed to find any reliable data regarding the normal blood levels of not only the population groups with which he was concerned but of any other tropical population groups In this matter tropical medicine was only a little way behind medicine in temperate countries where Wintrobe Haden and Osgood in America Witts and Price-Jones in England and others in these and other countries were trying to clear up the confusion that existed regarding normal hæmoglobin standards. This confusion was due mainly to the inadequacy of the apparatus used for estimating hæmoglobin and to the unsatisfactory practice of expressing results as a percentage of a variable and unknown normal standard so that the results of different workers were not comparable. However during the last decade figures from many sources have become available some of which are quoted below

Normal hæmoglobin levels.—It has been found that in almost every instance, whenever anæmia producing infections and gross dietary deficiencies can be excluded, the normal hæmoglobin levels in the different age and sex groups in tropical countries are not significantly lower than those of the corresponding groups in temperate climates. In the case of the European sojourner in India we found that the normal mean was distinctly higher than that of the standards given in British and American textbooks for example the normal for men was about 17 grammes of hæmoglobin per 100 c mm (124 per cent on the Haldane scale)

Normal standards of healthy native populations

Group	*Subjects and locality*	*Sex*	*Number in series*	*Mean and standard deviation*	*Authority*
1	Students Bombay	M	121	15.37 ± 0.96	Sokhey *et al* 1937-38.
2	Clerks and doctors Calcutta	M	30	15.70 ± 0.91	Napier and Das Gupta, 1936.
3	Students Bombay	F	101	12.99 ± 1.10	Sokhey *et al*, 1937-38.
4	Middle class age 14–30 Calcutta	F	128	12.63 ± 1.01	Napier Edwards and Das Gupta, 1941
5	——— Britain	M		15.60	Whitby and Britton, 1939
6	——— Britain	F		13.70	Whitby and Britton, 1939
7	Eastern U.S.A	M	61	15.80	Wintrobe, 1933
8	Eastern U.S.A	F	73	14.00	Wintrobe 1933.

On the other hand we found that in certain labour force groups much lower normal levels of hæmoglobin often existed Figures are given from a manganese mine where malaria was endemic and from tea-estate labour forces where both hookworm infection and malaria were prevalent the subjects were ordinary workers selected at random after, the grossly (clinically) anæmic individuals had been excluded. The manganese-mine recruits were mostly under nourished but showed no heavy parasitic infection.

Data from sub standard populations

Group	Subjects		Number in series	Mean and standard deviation
1	Manganese-mine recruits	men	47	13.74 ± 1.79
2	" workers		49	12.95 ± 1.72
3	Tea-estate, A		20	12.63 ± 1.41
4	B		26	12.00 ± 1.53
5	C		21	11.53 ± 1.67
6	B	women	25	10.40 ± 1.73
	D		20	10.80 ± 2.30

THE CAUSES OF ANÆMIA IN THE TROPICS

From the data given above it will be clear that climate *per se* does not cause anæmia What then are the causes of anæmia in the tropics? The anæmia varies in its degree and nature in much the same way as does the anæmia that occurs in temperate climates and it is susceptible to classification along the same lines.

Classification of anæmia —The causes of anæmia will be appreciated best if one remembers that the red blood corpuscles are like paper currency they are continuously being put into circulation they circulate for a time and eventually they wear out and have to be withdrawn In the circulation of the average man there are about twenty five million red cells and the duration of the life of a red cell is probably on the average about 75 days which means that in order to maintain the circulating red cells at a constant level about thirty three thousand million new red cells have to be produced by the hæmopoietic tissues daily to replace the thirty three thousand million obsolete ones that disintegrate or are otherwise withdrawn and disposed of by the hæmolytic tissues Production and destruction have to be balanced and any blood loss from the circulation has to be made good The body is capable of considerable adaptation but if there is failure of production, if there is excessive destruction or if there is any considerable loss of blood anæmia must eventually result therefore anæmia may be caused by (*a*) errors of erythrogenesis (*b*) loss of circulating blood or (*c*) errors of erythrolysis and it will be convenient to classify the cause of anæmia under these three major headings

The following table (Napier 1936) gives a pathogenetic classification of the anæmias in general with examples of recognized syndromes in which the anæmia of each particular group occurs Many of these examples are cosmopolitan diseases but wherever appropriate a tropical disease is included

Specific causes of anæmia in the tropics.—These are (*a*) infection (*b*) dietary deficiencies or more commonly a combination of these two causes and (*c*) congenital defects It will be convenient to consider the subject under these three headings with the full appreciation of the fact that the division is an artificial one

In the appropriate places in this book reference has usually been made to the blood picture in the diseases in which anæmia is a prominent symptom but it will be worth reconsidering the subject here

ANÆMIA DUE TO INFECTIONS

Malaria —This is probably the most important source of anæmia in the tropics The most obvious cause of the anæmia is the destruction

TABLE

Main group	Sub-groups	Examples of syndrome	General character of blood picture	Principles of treatment
I	A Aplastic or hypoplastic toxic or mechanical origin due to —			
ERRORS OF ERYTHROGENESIS	(i) unknown causes,	Idiopathic aplastic anæmia	Usually normocytic normochromic reticulocytes—few van den Bergh—neg.	*Remove cause* *Transfuse* to tide over critical period and in extreme cases repeat periodically to supply blood needs
	(ii) (a) bacterial or other parasitic toxins,	Anæmia of many acute and chronic infections, including tropical diseases, *e.g. relapsing fever* and *Malta fever*		
	(b) metabolic toxins,	Anæmia of nephritis		
	(iii) chemical and physical poisons,	Anæmia caused by benzol, lead, sulphonamides, radium and *x*-rays.	urobilin—absent	
	(iv) mechanical interference with blood formation	Carcinomatosis, Albers-Schonberg disease *anæmia of kala-azar*		
	(v) exhaustion of the bone-marrow	Terminal condition in many hyperplastic anæmias.		
	B Nutritional dysplasias.			
	(i) Iron deficiency			
	(a) Actual	Hypochromic anæmia of infants, invalids and others	Microcytic hypochromic reticulocytes—few van den Bergh—neg normoblasts—present urobilin—no increase	Supply excess of iron by mouth Ferrous sulphate, gr xviii daily for three weeks.
	(b) Relative.	Hypochromic anæmia of pregnancy and *hookworm infection.*		
	(c) Failure of absorption.	Simple achlorhydric anæmia		
	(ii) Deficiency of hæmopoietic *principle*		Macrocytic hyperchromic	Supply deficiency by giving liver extract.
	(a) Absence of intrinsic factor	Addisonian pernicious anæmia	(a) reticulocytes + megaloblasts van den Bergh + achlorhydria	(a) Refined liver extract parenterally or liver by mouth
	(b) Absence of extrinsic *factor*			
	( ) Actual.	*Idiopathic tropical macrocytic anæmia.*	(b) van den Bergh—neg and reticulocytes—few	(b) Crude liver extract and marmite
	(β) Relative or conditioned	*Tropical macrocytic anæmia of pregnancy*		
	(c) Failure of absorption	*Anæmia of sprue*	(c) urobilin—no increase iso- or hypochlorhydria	( ) Liver extract parenterally
	(d) Failure of storage	Anæmia of liver disease		
	( ) Failure of utilisation.	Achrestic anæmia		
	(i) Deficiency of vitamin C	Hypochromic anæmia of vitamin-C deficiency		

II	Due to hemorrhage external from mucous surfaces, or into serous cavities		The blood picture will depend on whether the hemorrhage is acute or chronic.	Stop bleeding and remove cause where possible
LOSS OF BLOOD FROM CIRCULATION, TRUE SECONDARY ANEMIA	A Following external or internal injury (acute)	Severed artery, ruptured spleen, etc	*Acute* normocytic normochromic reticulocytes ++	Transfusion
	B Associated with disease of tissues (chronic)	Hemorrhoids, gastric ulcer, hemoptysis, dysentery—amoebic, bacillary or metazoal vesical schistosomiasis	*Chronic* microcytic hypochromic reticulocytes + or ± van den Bergh—neg. *normoblasts*—present urobilin—no increase	Supply iron in excess and give good protein and vitamin diet
	C Associated with hemorrhage of [illegible]	*Scurvy*, snake (viper) bite		
	D Associated with blood-sucking parasites	*Hookworm*, *hirudiasis*		
III	A Conditions affecting red cells and making them more susceptible to normal lytic processes.			
ERRORS OF ERYTHROLYSIS	(i) Abnormal red-cell structure	Sickle cell anemia	*Normocytic or slightly macrocytic* normochromic reticulocytes ++ van den Bergh ++ urobilin ++ increased fragility of red cells.	When known and when possible remove cause *e.g.* malaria parasites by specific treatment. Provide hemopoietic substances in food protein vitamins and liver fraction.
	(ii) Abnormal physical condition of red cells, *e.g.* spherocytes	Acholuric jaundice, paroxysmal hemoglobinuria		
	(iii) Effect of toxins, chemical poisons, etc	Lead poisoning, arsenical drug poisoning.		
	(iv) Parasitization.	*Malaria* and *Oroya fever*		
	B Conditions causing over action of the erythrolytic tissues.	Chronic malarial splenomegaly, possibly *kala-azar*	ditto decreased fragility of red cells.	Remove cause. In chronic splenomegaly remove spleen.

of the red cells by the parasite that is it is a hæmolytic type of anæmia, due to the error of erythrolysis IIIA (iv) in the above classification, but there is evidence that the anæmia is disproportionate to the blood parasitization, so that some additional explanation for the anæmia must be found. Certain observations suggest that there is a toxin which depresses blood formation as long as the malaria infection is uncontrolled, so that it must also be classified as a toxic hypoplastic anæmia IA (ii) (a) in the table.

Further when there is very extensive red cell destruction especially if the patient has been repeatedly subjected to these attacks the blood forming material stored in the body becomes exhausted. Most of the iron is stored and re utilized but some of the other hæmopoietic elements apparently need replenishing, in such cases a macrocytic anæmia sometimes develops which does not improve spontaneously as the anæmia of malaria usually does once the infection is under control, but responds immediately with a sharp reticulocytosis when liver extract is given. This would bring the anæmia into the group of relative or 'conditioned nutritional dysplasias IB (ii) (b) (β)

It is frequently stated that the anæmia of chronic malaria is a hypochromic microcytic anæmia While the writer believes that this is largely a misconception through the frequent association of chronic malaria with other anæmia producing conditions *e g* hookworm disease and dietary deficiency, there is one possible source of iron loss that should not be overlooked namely the fixation of hæmatin in the form of insoluble hæmazoin pigment. It is therefore possible that in some persons on a low iron intake this source of loss may upset the iron balance and introduce an iron-deficiency element into the anæmia IB (i) (b)

Finally in certain persons subjected to malarial infection for many years through constant stimulation there is an overgrowth of the hæmolytic tissues in the body, *e g* in the spleen leading to a constant excessive destruction of red cells this places the anæmia in group IIIB

One might expect the anæmia of blackwater fever to show an iron-deficiency element in view of the loss of hæmoglobin that occurs through the kidneys apparently however the amount thus lost if it is insufficient to do irreparable damage to the kidney and kill the patient does not constitute a serious iron loss so that this element in the anæmia is overshadowed and a macrocytic anæmia that often necessitates the administration of liver extract (the conditioned nutritional dysplasia mentioned above) is the more usual result of a blackwater fever attack.

It is thus apparent that the anæmia of malaria is very complex and it is perhaps not surprising that writers have been reluctant to commit themselves to a clear cut statement as to what is the characteristic anæmia of this disease

In the malarial attack in the partially immune there is often little evidence of anæmia, which suggests that some immunity to the malarial toxin develops If such a person is given specific treatment for the malaria immediately the anæmia can usually be ignored However in the non immune adult and in children anæmia is fairly constant

The *degree* of the anæmia will naturally vary with the circumstances In a severe malignant tertian (*falciparum*) attack that is not brought rapidly under control the red cells may be reduced by as much as two millions per cubic millimetre in a few days, or in a blackwater fever attack in a few hours but the reduction is usually far more gradual and seldom so extreme.

Treatment —In the well nourished person with an acute malarial attack return to normal is usually spontaneous once the red cell

destruction and the toxin production ceases When in such a case the hæmoglobin fails to return to normal and there is a persistent reticulocytosis an early relapse of malaria may usually be anticipated the recognition of this residual anæmia is sometimes of diagnostic value when malaria parasites are scanty In the ill nourished and debilitated, it may be necessary to supply some of the blood forming elements in the form of liver extract marmite and even iron to ensure an early return to normal If the patient has been subjected to repeated attacks over a long period the hæmolytic tissues are hypertrophied and disorganized and in order to adjust the dyscrasia and balance hæmopoiesis whole liver principle (crude liver extract) may have to be given as in the previous case And finally in extreme cases it may be advisable to remove or put out of action a large portion of the reticulo-endothelial system by removing the spleen or tying the splenic artery

Ankylostomiasis—This is probably the second most important source of anæmia in the tropics The cause is almost entirely blood loss from the bowel as a result of the profligate blood sucking by the adult worm this makes it a true chronic secondary anæmia IID, which is usually markedly microcytic and hypochromic. In heavy infections no amount of dietary iron is sufficient to compensate for the iron loss but in moderate infections, the loss of blood is such that it could be compensated for if the individual were on good iron intake but when the subject is taking a diet containing only the minimal iron requirements this extra loss is sufficient to upset the balance and produce an anæmia that can be classed as a conditioned iron-deficiency anæmia, IB (i) (b)

However even when an excess of iron is given there are some instances in which the hæmoglobin level does not reach normal, so that there is possibly a toxic element also in this anæmia which would place it in group IA (ii) (a) The degree of anæmia may be very extreme and there are few conditions other than ankylostomiasis and hæmorrhage that will produce a microcytic hypochromic anæmia of this degree when the hæmoglobin is as low as 2 grammes per 100 c cm in a patient obviously not *in extremis* this infection should always be suspected.

Return to the normal hæmoglobin level follows adequate iron administration even without worm removal except in the few instances referred to above. The worms must however be removed or the anæmia will return (*see* ANKYLOSTOMIASIS)

Kala azar.—The most striking pathological reaction in this infection is a very considerable proliferation of the reticulo-endothelial tissue throughout the body This proliferation is very pronounced in the bone marrow and in that confined space it crowds out and depresses the activity of the hæmopoietic tissue, this places the anæmia in group IA (iv)

On the other hand, the activity of the macrophages is stimulated so that they phagocytose red cells actively and excessively The fact that the van den Bergh reaction is usually positive, and that there is a distinct reticulocytic increase suggests that this second cause of the anæmia group IIIB is not a negligible one Other possible causes of anæmia in kala azar are toxic depression of the bone marrow and liver dysfunction.

Under specific treatment for kala azar the reticulocytes return to normal and there is a steady improvement in the blood picture but the normal may not be reached for several weeks The administration of hæmatinics does not usually cause any material increase in the rate of improvement.

Oroya fever—The anæmia in this condition parallels that of malaria and is mainly due to the parasitization of the red cells however the mechanism is slightly different as the bartonella infection does not

apparently cause the red cell to rupture and disintegrate but damage it so that it is phagocytosed prematurely This anæmia is thus classified as IIIA (iv)

Trypanosomiasis.—Anæmia is not usually marked in the early stages of the disease, and any anæmia that occurs is probably of toxic origin. In the later stages in native patients it is often very striking and is certainly mainly nutritional in origin This class of patient becomes lethargic and indifferent to his dietary needs, and lacks the energy to work to earn his food.

Acute febrile conditions—The mechanism of the anæmia is not very clear in most of these conditions though a degree of anæmia is common. One must conclude that the anæmia is mainly due to a toxic hypoplasia IA (ii) (a)

In the typhus fevers anæmia is not usually prominent but it may be considerable after a severe attack of Rocky Mountain spotted fever this is probably due to the extensive hæmorrhages that are likely to occur and it can be placed in group IIC

In *yellow fever*, *Weil's disease* and *relapsing fever* again anæmia is not usually prominent The jaundice that occurs is not hæmolytic in origin but hepatic, and it is due to the failure of the damaged liver cells in disposing of the products of the normal quota of destroyed red cells. Such anæmia as occurs must also be toxic in origin.

In *brucellosis* the anæmia may be considerable in proportion to the severity of the disease This suggests that there is a specific action by the bacterial toxins on the hæmopoietic tissues and the anæmia must be grouped as IA (ii) (a)

Dysentery—Any severe dysentery whether it is caused by bacteria protozoa or metazoa may produce an anæmia of the true secondary type that is due to loss of blood IIB This of course may be acute but it is more frequently subacute or chronic

In the later stages of these infections the anæmia is due mainly to malabsorption it is a nutritional dysplasia IB either sub-group (i) (c) or (ii) (c) usually both elements being apparent.

In chronic amœbiasis, it has been suggested that the anæmia is due to toxic absorption from the intestinal tract, but the evidence for this is not entirely satisfactory this would place it in group IA (ii)

The anæmia of amœbic hepatitis and liver abscess is often very marked it is usually normocytic or macrocytic It can be classified as IB (ii) (d) As the bowel condition improves the blood picture returns slowly to normal but the rate of improvement is accelerated considerably by the administration of liver extract and in some cases this must be considered an essential part of the treatment.

Other helminthic infections.—*Diphyllobothrium latum* has been reputed to cause a pernicious anæmia like anæmia but the causal relationship of this worm to the anæmia is still in question. However a fatty acid that is capable of causing a macrocytic anæmia in experimental animals has been isolated from this worm it is therefore possible that this anæmia is a hypoplastic dysplasia of toxic origin, IA (ii) (a)

The schistosomes produce an anæmia of the secondary type by causing blood loss in the bowel and bladder but there is evidence that they also are capable of causing some anæmia by their toxins in the earlier stages of the infection, and in the later stages by the damage to the bowel, which will cause failure of an absorption of essential hæmopoietic substances and to the liver which will cause failure of their storage

ANÆMIA DUE TO DIETARY DEFICIENCIES

Tropical macrocytic anæmia

History.—In 1929 under the title 'malignant anæmia of the tropics' Mackie drew attention to an anæmia which he had observed twenty years earlier that was common amongst both men and women in Bombay. Two years later Wills (1931) showed that a macrocytic anæmia which was particularly common amongst pregnant women but which also occurred in non-pregnant women, was curable by the oral administration of autolysed yeast (marmite). She called the condition 'tropical macrocytic anæmia' and considered that it was primarily a nutritional condition.

These two writers were obviously describing the same condition. Mackie who was writing his paper from notes that he had made many years before, did not give much in the way of hæmatological data except regarding the degree of the anæmia and the statement that in about half the cases the colour index was above unity but Wills claimed that her anæmia was a macrocytic non-hæmolytic anæmia.

Napier (1936) pointed out that all macrocytic anæmias occurring in the tropics and responding to marmite or liver extract were not the same and that there was a hæmolytic type of macrocytic anæmia that was usually associated with a large spleen possibly of malarial origin. Fairley and co-workers (1938) reporting observations in Macedonia, suggested the name 'nutritional macrocytic anæmia' and confirmed the observation that there was a hæmolytic and a non-hæmolytic type. It was shown that this anæmia did not respond—in the way that pernicious anæmia does—to moderate doses of purified liver extract, e.g. anahæmin (Napier 1938, Wills and Evans 1938) but later it was found that there may be a brisk response to large doses of anahæmin (Napier 1938, Foy and Kondi 1939). Subsequently workers in many tropical countries described macrocytic forms of anæmia that were distinguishable from pernicious anæmia on the one hand and sprue on the other.

Ætiology.—It is possible that in a few instances tropical macrocytic anæmia (T.M.A.) is a pure dietary deficiency but there is strong evidence that, in the majority of cases it is a 'conditioned deficiency' in which bowel disorder, malaria and other infections play a part. The deficient dietary substance has not been identified, but it is associated with the vitamin B_2 complex and is probably not a single fraction [see IB (ii) (b) (β) in classification table].

In tropical macrocytic anæmia hæmolytica there is always a history of repeated attacks of malaria in childhood and adolescence and there is usually a large spleen. Apparently there is overaction of the hæmolytic tissues which destroy red cells in excess; these have to be replaced, so that there is a greater demand for hæmopoietic substances than can be met by the low dietary intake of the patient and relative nutritional anæmia develops. The iron is recovered and re-utilized, so that the anæmia is of the macrocytic type; this anæmia can be classed as IIIB (see table).

Tropical macrocytic anæmia of pregnancy occurs amongst women of the poor-dietary classes usually with a previous history of dysentery and/or malaria; they are mostly vegetarians whose protein intake is low and though a particularly low vitamin B complex intake has not always been demonstrated, a marked improvement sometimes follows the administration of this vitamin in the form of marmite. However the absence of any appreciable response in the presence of the fœtus and the rapid recovery in all moderately severe cases after its removal at term or

prematurely suggest the possible action of a pregnancy toxin producing a conditioned deficiency

Another suggestion is that it is a relative deficiency like that known to occur in the case of iron deficiency in pregnant women, but the positions are not parallel because the infantile mortality is very high in TMA suggesting that the fœtus also suffers from a deficiency whereas in iron deficiency anæmia, the infant takes all the iron it requires and the infantile mortality is low

Thus to summarise tropical macrocytic anæmia may be (i) a pure dietary deficiency, (ii) it may be due to a combination of a poor diet and poor absorption when it is associated with a definite bowel syndrome such as sprue or para-sprue (iii) it may be due to a combination of a poor diet and repeated malarial infections, or (iv) it may be due to the super addition of pregnancy to any of these three causes or to any combination of them.

Epidemiology—Since this condition was first described several instances of the pregnancy form have been reported from temperate countries but it is nevertheless essentially a disease of backward tropical countries. It has been shown to be prevalent in India Malaya, tropical Africa the West Indies and South America and will probably be found to occur in every tropical country where it is sought.

It occurs mainly in the poor economic classes of the natives or settlers in tropical countries It may occur at almost any age, but it is more common in late adolescence and early adult life and partly because of the association with pregnancy is more common amongst women than men but it occurs in both sexes. It was more frequently observed in first and second pregnancies.

The condition shows seasonal variations. It was more prevalent in the second half of the year in India this appeared to be correlated with the lack of fresh vegetables and fish during the hot weather and monsoon (April to October)

Pathology—Our knowledge of the morbid anatomy of this condition is very poor and in the few post mortem examinations that have been performed the associated disease clouded the picture

Blood picture.—The anæmia may be extreme and figures as low as 500,000 red cells per c.mm. and 2 grammes of hæmoglobin per 100 c.cm. of blood are sometimes recorded though in the majority of cases the red cell count will not be much below 2 000 000 per c.mm. The red cells are macrocytic usually between 100 and 150 c μ the mean corpuscular volume is usually between 30 and 40 γγ and the mean corpuscular hæmoglobin concentration between 33 and 37 per cent, so that the anæmia is ordinarily a normochromic one. The Price-Jones curve is shifted to the right but it tends to retain its normal shape and is not usually a low spread-out curve like that of pernicious anæmia. Polychromasia and anisocytosis are usually observed but are not particularly marked. Normoblasts may be found but not megaloblasts.

Reticulocytes will average about 5 per cent in the hæmolytic form but will not be above 1 or 2 per cent in the other forms.

The leucocyte count is usually normal or slightly raised. The weighted mean of the modified Arneth count is below 2 0 There may be a slight relative increase of lymphocytes.

In the non hæmolytic forms the van den Bergh test will be negative, but in the hæmolytic forms the indirect van den Bergh test will show 1 0 milligramme or more of bilirubin per 100 c.cm and in severe cases the direct van den Bergh test may also be positive

The sternal puncture does not usually show the presence of true hæmoglobinized megaloblasts (Ehrlich's) but there is a considerable increase in the percentage of basophilic non hæmoglobinized primitive red cells with finely stippled highly-staining nuclei often referred to as megaloblasts.

Gastric acidity.—Acid is usually present but in the majority of cases there is some degree of hypochlorhydria.

Symptomatology.—The clinical picture naturally varies with the degree of the dyscrasia and the symptoms are basically those of any anæmia lack of energy breathlessness and palpitation on slight exertion pallor and swelling of the feet. In this condition, the conjunctivæ sometimes show a sub-icteric tinge and the mucous membranes are a faint lemon colour rather than the alabaster white of the patient with hypochromic iron-deficiency anæmia. The tongue may be sore and slightly denuded but the fiery red tongue of the pernicious anæmia patient is rare. There may be cardiac dilatation and hæmic murmurs but these are less pronounced than they would be in a case of iron-deficiency anæmia of the same severity. The pulse rate is usually rapid but fever is unusual.

In the hæmolytic cases the spleen (usually) and the liver (often) are enlarged.

The typical clinical picture will usually be overshadowed by the determining factor (e.g. bowel disorder and/or pregnancy) or other associated conditions.

Diagnosis.—Tropical macrocytic anæmia has to be differentiated (a) from pernicious anæmia and (b) from sprue and para-sprue.

(a) Pernicious anæmia which incidentally is rare in true natives of the tropics can be excluded by the presence of hydrochloric acid in the gastric juice, by the absence of hæmoglobinized megaloblasts in the sternal puncture smear and by the absence of appropriate reticulocyte response to refined liver extract (anahæmin) in ordinary doses as well as by the absence of many signs and symptoms of the true pernicious anæmia syndrome, e.g. the raw beef tongue (very rare in TMA) and the neurological symptoms.

(b) Sprue and para sprue can be excluded by the absence of the full syndrome of either of these conditions. It seems very probable that in *many cases of sprue the anæmia has the same ætiology as that of TMA*, but TMA is not a constant part of the sprue syndrome nor are most of the symptoms of sprue present in the majority of cases of TMA. The same is true with regard to para-sprue.

Prevention and treatment.—The disease does not occur amongst people living on a good mixed diet containing a sufficiency (100 grammes a day) of protein and an adequate amount of all the vitamins even in the presence of the other ætiological factors.

The treatment in the uncomplicated case is the provision of the missing fraction. Marmite (vegex), or some other form of autolyzed yeast, should be given in generous amounts, 30 grammes a day. This alone will effect a cure in a number of cases but it is often difficult to persuade a patient to take this amount, and there are cases which do not appear to respond therefore whole liver (lightly cooked) liver soup, or liver extract should be given as well. Some patients respond best to oral administration, others to parenteral. Campolon was in the writer's experience far better than any other liver extract for parenteral use. The refined

This is not now [illegible]ailable and no commercial substitut[illegible] appears to contain [illegible]xactly the same liver fractions.

tracts (e g anahæmin) have to be given in large doses (200 mg. daily) be effective.

When pregnancy is the determining factor marmite and liver extract ould be given in generous doses but the response may be disappointing itil pregnancy is terminated In severe cases, and even in moderately vere cases prior to parturition a blood transfusion will help to tide over critical period.

In the hæmolytic form anti malarial treatment will not usually hieve anything as the infection may not be active but reduction of the æmolytic bed by *removal of the spleen, or by tying the splenic artery,* ten produces a considerable improvement.

Prognosis —In the pure dietary-deficiency cases this is excellent, but the 'conditioned' cases, this will depend on the conditioning factor pregnancy if TMA is diagnosed early and treated vigorously it is ten possible to carry pregnancy to full term. Later unless the patient very near full term it is usually impossible to effect improvement witht inducing abortion or premature labour In very severe cases, even is may be unsuccessful The infantile mortality is very high It was per cent in one series (Napier Edwards and Das Gupta *loc. cit.*)

In the hæmolytic cases repeated relapse is common and the prognosis on the whole not good.

SPRUE

While the exact ætiology of this disease is still in doubt, it is nost certainly not due to a specific infection it is now usually classi d as a dietary disease but the writer believes that it has its basis in 'inborn error of metabolism' The anæmia is probably due to ılabsorption of essential blood-forming elements especially of the æmopoietic principle The anæmia is usually macrocytic and is classid as IB (ii) (c)

This anæmia may respond to liver extract by mouth, but a much ore satisfactory response is usually obtained when liver extract is given renterally and in fact in some cases this seems to tip the balance and use a complete remission of all symptoms although in the fully veloped syndrome dietetic treatment also is necessary

ANÆMIA DUE TO CONGENITAL DEFECTS

Sickle-celled anæmia which is confined to negroes though most of the idies of this disease have been made in North America amongst the ttled negroes in that country, is perhaps the most striking example of tropical anæmia of congenital origin. Cooley's anæmia has less claim be considered tropical this disease again has been studied mainly in e United States but nearly all the subjects have been of Mediterranean ock, Italian Greek, American and Syrian. However several cases have en reported from India. Reference should perhaps be made again here sprue this disease occurs mainly, possibly only, in individuals of the cial stock of cold countries but it usually develops when the subject es in a tropical climate.

A short description of the former two conditions will be given here.

Sickle-celled anæmia.—This disease must not be confused with the kle-cell trait, a condition relatively common amongst individuals of gro stock, occurring in 7.3 per cent of 8 453 negroes (Diggs *et al.* 1933) t not necessarily associated with any morbidity this trait is transtted *hereditarily* as a dominant Mendelian characteristic,

Sickle-celled anæmia occurs in about 1 in 40 negroes with the sickle-cell trait. Few authentic cases have been reported in persons without some admixture of negro blood. The condition has been diagnosed during the first year of life most patients come under observation during the first two decades and they seldom survive the third decade

Pathogenesis —The sickling phenomenon is associated with reduction of the hæmoglobin in the cell *in vitro* and apparently *in vivo* as for example when a local anoxæmia is caused by constriction of a finger, the shape of the red cell can be restored by oxygenation of the blood When this occurs in the tissues stasis results and occlusion may follow Many of the symptoms for example pain in the spleen and elsewhere heart changes, secondary pulmonary changes and ulceration in the legs may be caused by vascular occlusion in different organs and tissues The compensatory hyperplasia of the bone marrow will account for the bony changes

The hæmolytic blood picture and the anæmia are caused by the early hæmolysis of the defective sickle cells which in turn leads to the vicious cycle of anoxæmia and further sickling This anæmia may be classified as IIIA (i)

Blood picture.—The red cells are reduced to 2,000,000 or even 1,000 000 per c.mm and the hæmoglobin percentage proportionately The mean size and colour of the cells are usually within the normal range though there are almost always both macrocytes and microcytes present. The reticulocyte percentage is between 5 and 25 per cent. Normoblasts are constantly present from 1 to 10 per 100 leucocytes There are usually a few sickle cells present but if a sealed wet preparation is made the majority of the cells will develop into the sickle or some other bizarre shape within a few hours

There is a leucocytosis with a large mononuclear increase and a left ward shift in the Arneth count.

The indirect van den Bergh reaction is strongly positive.

Symptomatology —The patient may suffer from a considerable degree of anæmia before any special symptoms develop and there is usually a history of periodic attacks with periods of symptom free intermission.

The main symptoms beyond those directly attributable to the anæmia namely weakness and breathlessness on exertion, are fever—which may be a low irregular fever or rise to 103 or so pains in the joints pains in the abdomen—that may simulate an acute abdominal emergency enlarged and painful spleen cardiac dilatation various neurological manifestation chronic leg ulceration—similar to varicose ulcers and bony deformities—sabre tibia scoliosis and kyphosis

Roentgenological examination of the bones shows osteoporosis or osteosclerosis and hair-on-end thickening of the skull In the retina there is a very marked tortuosity of the vessels

Diagnosis.—Sickling alone is not evidence of sickle-celled anæmia, but in sickle-celled anæmia if the blood is taken from a vein with an air free syringe (dead space filled with liquid paraffin) and injected into 10 per cent neutral formaldehyde in 0 85 per cent saline 30 to 60 per cent of the cells will be sickled whereas only an occasional sickled cell will be found if the patient simply has the sickle-cell tendency

Treatment.—This is symptomatic only

Prognosis —This is always bad temporary improvement will often occur but death usually occurs within the first three decades

Cooley's anæmia —This syndrome has recently been separated from the more comprehensive von Jaksch's syndrome As indicated above it was first believed to be confined to individuals of Mediterranean stock

but has recently been reported in several Indian children (Napier Shorten, and Das Gupta 1939) and one Chinese (Foster 1940)

The most characteristic feature of the disease is the bony changes. In the long bones there is an increase in the medulla with thinning of the compact bone The general decrease in the density of the medulla leaves the trabeculæ standing out forming a characteristic mosaic pattern in the *x* ray picture. In the skull the diploe is thickened to several times its natural thickness with perpendicular striations standing out to give the appearance of hair standing erect on the inner plate of the skull, the outer plate being invisible

The blood picture is less characteristic and has features common to other examples of the von Jaksch s syndrome The degree of anæmia is variable but often considerable The erythrocytes vary considerably in size from extreme microcytosis to extreme macrocytosis but the mean corpuscular hæmoglobin is low, so that the anæmia is hypochromic There are frequently target cells present and many of the red cells are distorted and fragmented There are many nucleated red cells mostly normoblasts, and always a distinct and sometimes a marked—up to 50,000 per c mm.—leucocytosis. The van den Bergh reaction indirect is usually positive

The anæmia and the large head are the most striking clinical features. The steady progress towards a fatal termination is usually uninterrupted. If the symptoms appear in the first year of life death usually occurs within six months if however they do not appear until later the child may survive several years Death is usually due to intercurrent infection.

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RABIES

Definition.—Rabies or hydrophobia is a zootic disease which is potentially world wide in its distribution but has been excluded from certain countries and entirely banished from others. It is however always a serious problem in the tropics. It is caused by a filtrable virus which is transmitted to man by the bite of carnivores usually canines. The virus spreads along the nerves, and the symptoms are mainly of a nervous nature: excitation and/or depression, and later paralysis. When the symptoms are established, the disease is invariably fatal.

Epidemiology.—One of the reasons for the relatively heavy incidence of rabies in the tropics is the presence of innumerable stray dogs and of other actual and potential reservoirs of infection, for example jackals, foxes and mongooses in India, and vampire bats in Brazil, Trinidad and Jamaica. Another cause is the general administrative and sanitary backwardness in these countries.

The disease is very widespread in India and in the Pasteur Institute in Calcutta, which is only one of several such institutes in the country, as many as 10,000 persons undergo anti rabic treatment annually. It is also very prevalent in Africa and South and Central America.

The disease has apparently never been introduced into Australia; this is the result of rigid quarantine rules aided possibly by the absence of any potential wild reservoirs of infection. It was banished from Great Britain by the rigidly enforced muzzling orders of half a century ago as well as by the adoption of a six months quarantine period for imported

dogs but was temporarily reintroduced after the first world war apparently by the returning soldiers dogs which evaded the quarantine regulations In the United States between fifty and sixty deaths from rabies occur each year where the control problem is admittedly a complex one on account of its many miles of land frontier

There is a popular superstition that the disease is confined to certain seasons of the year especially the late summer days There is no statistical support for this belief

Ætiology.—The causal organism is a medium sized filtrable virus about 125 millimicrons in diameter For infection to occur the virus must reach the nerve tissue it cannot therefore be transmitted through the unbroken skin or mucous membrane.

By repeated sub-passage of the virus directly on to the brain of a series of rabbits or sheep it is possible to change an ordinary street virus with its long and inconstant incubation period, into a virus with a fixed incubation period of three to six days After attenuation—by one of several recognized methods—this fixed virus introduced subcutaneously into man is usually innocuous but retains its antigenic properties

Most animals are susceptible to infection, but not all are capable of transmitting it by their bite This is probably true of the large herbivora that are frequently infected in some countries As far as man is concerned, dogs, jackals cats and possibly vampire bats are the only important transmitters of infection though other animals may act as regional reservoirs of infection In the United States during 1941 out of 7,877 cases of rabies 6,648 were in dogs The dog may have the virus in its saliva 3 to 4 days before symptoms of the disease appear and it remains infectious until it dies death usually occurring within six days of the onset of symptoms

Pathogenesis.—The virus spreads up the nerve trunks until it reaches the cord from which point its spread is both centripetal and centrifugal Spreading along the efferent nerves the virus reaches the nerve terminals in many organs in the body and infected nerve ganglia are shed into the secretory fluids *e g* the saliva. Symptoms do not appear until the central nervous system is involved hence the incubation varies considerably from under 30 days to over 60 days according to the distance of the point of entry from the central nervous system In the brain it produces an encephalomyelitis

The most characteristic specific changes are produced in the pyramidal cells of the hippocampus major where the specific Negri bodies are most readily found though they are often present in other nerve cells in the brain Negri bodies are acidophilic bodies observed in the cytoplasm of the nerve ganglion cell they vary considerably in size and shape usually being 3 to 10 microns in diameter and round or oval in shape, and are granular in appearance Negri bodies are not parasitic structures but result from the reaction of the cell to the virus and are comparable to the inclusion bodies that are seen in various parenchyma cells in other virus infections

Symptomatology.—The incubation period is from two weeks to six months this is influenced by several factors including the site of the bite (*vide supra*) The onset is usually preceded by a day or so of malaise headache insomnia irritability and slight fever or the onset may be sudden, with the development of periods of restlessness anxiety and hyperexcitability Breathing becomes rapid, and air hunger may develop These periods of excitement alternate with periods of calm but the former tend to become longer and soon are accompanied by actual spasms of muscle groups such as those of deglutition These spasms are precipitated

when the patient attempts to drink, and in his thirsty state even the sight or thought of water may cause the spasmodic retraction of the head in a *series of jerks* Spasms are also precipitated by other stimuli such as a light touch noise or even air movement. These spasms alternate with periods of complete normality, when the patient's mind is clear and he talks perfectly rationally about his condition. Later the spasms are replaced entirely by paralysis which is at first local but eventually becomes generalised. Sweating and salivation are increased and the mouth is often filled with a ropy and frothy mucus There is often a low fever

Eventually the patient sinks into a paralysed and weak state and death follows or this may occur suddenly during one of the spasms, within 2 to 3 days of the onset of symptoms

Other types have been described including a form in which paralysis develops from the onset and simulates acute ascending myelitis.

Diagnosis —The combination of the history and the clinical picture are usually sufficient to make a diagnosis certain, but hysteria malingering, tetanus, meningitis encephalitis and poisoning, and in the paralytic type, other paralyses *e g* Landry's may have to be excluded

Post-mortem diagnosis may be made in man or dog by examination for Negri bodies and by animal inoculation Both impression and crushed preparations of Ammon's horn in the hippocampus major in the floor of the lateral ventricle and of the oculo-motor nucleus should be made stained by Giemsa's method and examined for Negri bodies (*vide supra*)

Cerebral inoculations of mice should also be made Webster (1942) recommends the following procedure —

'A bit of Ammon's horn of the suspected animal is emulsified by grinding it in a mortar diluted about 20 times with sterile water or broth, and injected in 0.33 c cm quantities through the skulls into the brains of eight 2 to 3 weeks-old Swiss mice. In case the suspected material is *contaminated it may be immersed for several hours in 10 per cent ether* and then injected intracerebrally or into the gastrocnemius muscle in 0 02 c cm volumes. On the 5th 6th and 7th days, respectively one mouse is sacrificed and its brain examined for Negri bodies *according to the techniques described above. The remaining mice are observed for 20 days* for signs of rabies Mice developing lower limb paralyses and becoming prostrate are sacrificed and their brains tested for Negri bodies.

If the suspected material really contains the rabies virus the mice usually show Negri bodies on the 5th or 6th day become sick on the 7th to 10th days, and die on the 9th to 12th days. They are generally uniform in their response—either nearly all become sick and die or all remain well. *Rarely do the mice remain well for periods of 15 days* and then develop rabies.

Great care should be taken to avoid self infection while carrying out these examinations

Whenever possible expert advice should be obtained and if examination is to be carried out elsewhere, the whole brain in the case of man and the whole head in the case of the dog should be sent in a suitable receptacle to the laboratory on ice—not on dry ice

PREVENTION

Control of rabies in animals.—This is first a matter of wise legislation and then rigid enforcement of the laws made. Six months quarantine for imported dogs the licensing of all dogs and the destruction of all stray (unlicensed) dogs and the muzzling of all dogs while at large or in any public place whenever there is a rabies epizootic have successfully controlled this disease in several countries. Compulsory inoculation of

dogs has also been adopted with success. It may be necessary to main tain these control measures over long periods and some of them of course permanently especially when there is a danger of reintroduction of infection by wild carnivores but rabies is an essentially controllable disease and should be controlled

Control of the infection in man —When an individual is bitten by a dog that is known or suspected to be rabid the wound should be cleaned immediately and *cauterized* After protecting the skin with vaseline this may be done carefully with fuming nitric acid or pure phenol which should be washed out with sterile saline powdered potassium permanganate can also be used. The extent of the cauterization must depend on the site of the bite and on the chance of the dog s being rabid While it must be admitted that unsightly scars have often been produced unnecessarily there is considerable evidence that skilful cauterisation is of value Cauterization must not be used as an excuse for neglecting anti rabic vaccination.

Anti rabic vaccination should be carried out as early as possible in every case of effective bite by a dog which is known to be rabid Before this step is taken a determined effort to find out whether or not the animal was rabid should be made. When it can be caught it should be shut up and kept under observation and if it dies within 10 days or shows obvious signs of rabies and has to be destroyed the brain must be examined or sent for examination for evidence of rabies if it survives this period, it may be assumed that it was not rabid.

The rabid animal —The first evidence is a departure from normal behaviour and disposition. An unusual display of affection or the reverse a withdrawal from human and canine company irritability and snappiness should arouse suspicion. Later the animal will often run amok biting everything and everybody and uttering a shrill meaningless bark. An unsolicited bite from a dog should always raise suspicion and when it is from a jackal it may be assumed that the animal is rabid. The animal s lower jaw sometimes drops and it dribbles saliva As opposed to the *excitable or furious* form of the disease a paralytic form also occurs and the first sign may be difficulty in swallowing often diagnosed as a bone in his throat.

Many febrile conditions such as distemper will cause cerebral symptoms especially in the young dog these symptoms may include irrational behaviour with apparent aural and visual hallucinations which will often simulate rabies.

The virus is present in the salivary glands of a dog 3 to 4 days before it shows evidence of rabies

Indications for vaccination.—Whether anti-rabic vaccination is begun immediately or whether a report on the dog is awaited will depend on cir cumstances the probability of the dog being rabid and on the nature and location of the bite In the case of severe bites on the upper limb and face treatment should be begun immediately if there was any possibility that the animal was rabid the same applies to any effective bite if there is strong evidence that the animal was rabid. On the other hand if the animal is under observation and the bite is a slight one through clothes or on the trunk or lower limbs it will be safe to await the verdict on the condition of the dog Further when a dog under observation is declared non-rabid any course of treatment commenced can be discontinued

The virus does not enter through the unbroken skin so that licks and other contact with rabid animals are not an indication for anti rabic vaccination It i however the practice in most Pasteur Institutes in India at least to advi_e anti rabic vaccination for any one who has had

any direct contact with a rabid or supposedly rabid animal It is difficult to criticize this cautious attitude but perhaps the time has come for a greater display of moral courage The treatment is expensive and not entirely without risk.

Anti rabic vaccination—Many types of vaccine both dead and alive, have been used. There is considerable evidence that the best and most economical to prepare on a large scale is phenolized sleep vaccine made up as a 1 per cent emulsion of sheep's brain. It is given subcutaneously in doses of 5 c cm. daily for 14 days During the course of injections, the patient is advised to take only light exercise and to avoid alcohol.

The only post-vaccinal accident, other than the avoidable ones due to sepsis is paralysis varying from that of a localized group of muscles to an ascending paralysis of the Landry type This sequel only occurs in about one in ten thousand cases when killed vaccine is used although more frequently with live vaccine The difference suggests that many of the latter cases are examples of fixed virus rabies. It is very rarely fatal.

Treatment.—No specific treatment of the slightest value has yet bee discovered

The patient should be put to bed in a darkened room, protected from all external stimuli and kept under the influence of sedatives and anti-spasmodics of the latter the classical one is atropin. Sedatives have to be administered in particularly large doses if they are to produce their effect.

Prognosis.—Experience indicates that once symptoms have developed, the infection cannot be overcome and a fatal issue is inevitable. It must however be appreciated that there are many factors, namely, the position and depth of the bite the genus of the biter (jackal bites are more frequently fatal than dog bites) the interposition of clothing, and the infectivity of the bite to be taken into account and it has been diversely estimated by different observers that from 2 to 80 per cent of all persons actually bitten by rabid animals if untreated would develop the disease. The present-day opinion is that the figure is about 10 per cent, and that efficient anti rabic treatment will reduce the death rate in these persons, as a group to about 2 per cent, but here yet another variable factor comes in the time after the bite at which treatment is given. Most Pasteur Institutes give a lower death rate than this but their figures are usually diluted by a large number of persons who were not bitten at all or who were bitten by non rabid animals.

* The importance of this factor is well brought out in a recent report of the Pasteur Institute of Bengal attached to the Calcutta School of Tropical Medicine an analysis of the Indian patients who underwent treatment during 1930 shows the following —

Position of bite	*Number treated*	*Deaths*	*Death rate*
Leg	3,203	12	0.375
Trunk	164	0	
Arm	1,877	16	0.85
Head	250	11	4.40

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Position of bite	*Number treated*	*Deaths*	*Death rate*
Leg	3,203	12	0.375
Trunk	164	0	
Arm	1,677	16	0.85
Head	250	11	4 40

REFERENCES

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* Not referred to specifically in the text.

A NOTE ON MYIASIS AND SCARABIASIS*

MYIASIS

AT times invasion of the tissues and organs of man and other animals by fly maggots may take place This condition is comprehensively known as myiasis

The screw worm larvæ of *Chrysomyia bezziana* will infest the natural orifices of the human body such as the ear mouth, eye, nose, and vagina and cause considerable destruction of tissues Myiasis due to *Cochliomyia hominivorax* is common in man in tropical America

The flesh fly, *Sarcophaga* generally causes external myiasis. The larvæ are deposited on gangrenous sores lacerated wounds etc and being saprophagus in their habits they bring about a rapid healing of the ulcers. Larvæ of *Sarcophaga* sp and of *Chrysomyia megacephala* have been successfully employed in the treatment of cellulitis and osteomyelitis in India, whereas in America larvæ of *Lucilia sericata Phormia regina*, and *Calliphora erythrocephala* grown in a sterile condition have been employed for artificial maggot therapy

Cutaneous myiasis is often caused by larvæ of bot-flies subcutaneous tumours are generally produced. The maggots of sheep bot-flies *Oestrus ovis* have been found in the conjunctiva and nasal cavities of man in the Central Sahara.

Intestinal myiasis is to a great extent accidental the larvæ being swallowed with food. The frequency with which 'rat-tailed' larvæ of the drone fly *Eristalis tenax* occur in liquid excrement should make one extremely cautious in accepting the numerous reports of these larvæ being evacuated with the stools There are however several cases on record in which untoward symptoms such as indigestion constipation emaciation and dysentery could be associated with these larvæ in the intestine

SCARABIASIS

SCARABIASIS or beetle-disease is caused by the invasion of the intestine by dung beetles this occurs particularly in children. It has not been reported in sucklings and only once in an adult. Only those who have cut their teeth and are able to take solid food are affected.

The reports usually state that the insects are passed with the fæces at intervals which may extend over some months The passing of the beetles is generally associated with symptoms of failing health such as loss of appetite occasional diarrhœa dysentery progressive emaciation and sometimes there are slight rises of temperature The stool is usually semi-solid, never hard and after it has been voided the attention of the mother is attracted to some movement in it a beetle gradually works its way up to the surface emerges and flies away As a rule the infestation is by more than one beetle, and sometimes over a period of months large numbers are passed the health of the child improving in the intervals. Strickland and Roy (1939) have discussed at length the method by which these insects gain access to the alimentary canal and they believe that the infestation takes place per anum.

Instances have been reported from the eastern parts of India and Ceylon also from South Africa

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STRICKLAND C and ROY D N (1939) Scarabiasis or the Presence of Beetles in the Intestine. *Indian Med. Gaz* 74, 416.

* By D N Roy M D Professor of Entomology Calcutta School of Tropical Medicine also director

SNAKES AND SNAKE BITE*

SNAKES

SNAKE BITE

*By the author and Dr S. K. Ganguli M.B. Assistant Professor of Entomology Calcutta School of Tropical Medicine. The large table was prepared by Dr Ganguli but has been modified slightly by the author with reference to certain American species of snakes.

SNAKES

Introduction —The practical importance to the ordinary practitioner of any knowledge regarding snakes and snake-bite is often questioned by the logically minded. It is difficult to refute their arguments on statistical grounds as the annual incidence of fatal snake-bite (outside India) is less than 0 005 per mille and probably not one-tenth of the subjects will have been within the reach of medical aid. Nevertheless a practitioner in the tropics with no knowledge of snakes will not only feel himself ill equipped, but perhaps once during his life he will encounter a case in which a better knowledge of snakes might have helped him to save a life, and he will certainly often find himself in the embarrassing position of being quite unable to make even a reasonable guess as to whether or not a snake brought to him for identification is poisonous.

Further it is the duty of a practitioner in a tropical country to familiarise himself with the commoner snakes in the locality and this he cannot hope to do without a knowledge of the essentials of herpetology This study is important from two points of view—firstly in order to be able to recognise and avoid or destroy the poisonous snakes and secondly, to exonerate the non poisonous ones so that they may not be destroyed unnecessarily but rather encouraged, as they are often useful members of the local fauna in that many of them kill or frighten away rodents and also smaller poisonous snakes.

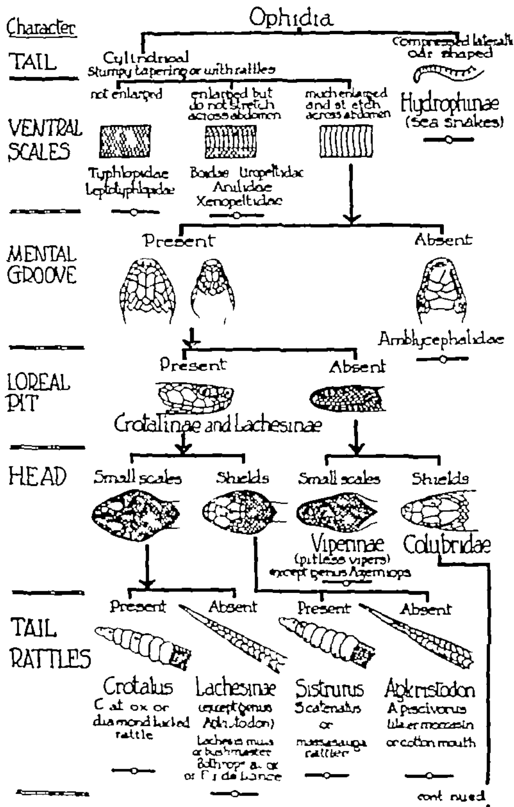
CLASSIFICATION

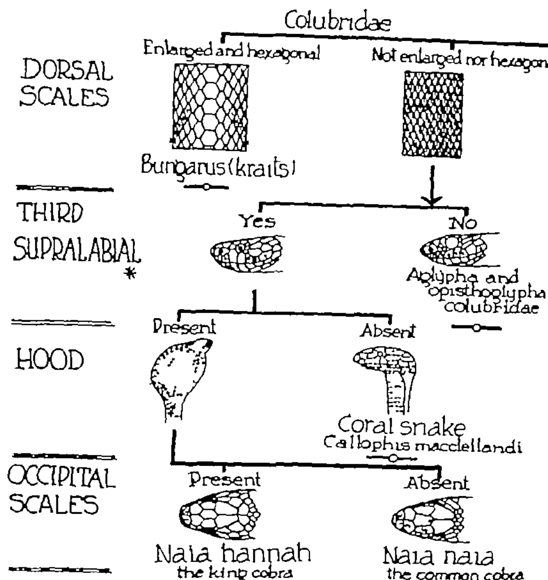
Snakes belong to the class REPTILIA.

The class REPTILIA is divided into twelve orders of which eight are extinct Extant reptiles belong to four orders —

1 Crocodilia—crocodiles alligators and gavials.
2 Chelonia—tortoises turtles and terrapins.

Identification of Poisonous Snakes





* The third supralabial scale touches both the eye and the nasal scale in the poisonous Colubridæ

Key Where the name is printed in large type it indicates that the species is a poisonous one, or if it is the name of a family subfamily or genus that all or many of its members are poisonous

For example all HYDROPHINÆ or sea-snakes are poisonous so are Crotalinæ Lachesinæ and Viperinæ Colubridæ contain both poisonous and non-poisonous species.

On the other hand the Typhlopidæ etc are non-poisonous so are the Amblycephlaidæ Of the Colubridæ, Bungarus, *Naia hannah* and *Naia naia* are very poisonous. Coral snakes are poisonous but not so highly poisonous and the aglypa and opisthoglypha Colubridæ are non-poisonous

(If the diagram is copied for class purposes the poisonous snakes should be printed in red ink)

3 Rhynchocephalia—represented by a single living species the Tuatera or Sphenodon (*Hatteria punctata*) of New Zealand a lizard like reptile in which the traces of the median eye can still be made out.

4. Squamata—snakes lizards and chameleons

The order Squamata is divided into three sub-orders of which two are still extant namely —

(i) Ophidia (or Serpentes)—snakes

(ii) Lacertilia—lizards and chameleons

In the sub-order Ophidia (snakes) about 2 400 species have been described of which over 300 are sufficiently poisonous to cause fatal effects in man. In India, including Burma and Ceylon there are at least 330 species of snakes of which about 70 are poisonous to man (40 terrestrial and 30 marine species) this is the only country in which all the families and sub-families are represented

There are nine families (1) Typhlopidæ (2) Leptotyphlopidæ (3) Aniliidæ (4) Boidæ (5) Uropeltidæ (6) Xenopeltidæ (7) Amblycephalidæ, (8) Colubridæ (9) Viperidæ

The family *Boidæ* includes several of the largest constrictor snakes. In it there are two sub-families Pythoninæ and Boinæ the former includes *Python reticulatus* the regal python the largest snake in the world, which attains a proven length of 33 feet and the latter *Constrictor constrictor* the boa-constrictor The Boidæ are not poisonous but kill their larger prey by coiling around them and crushing them

All the species of the first seven families are non poisonous the last two families include all the poisonous snakes The *Colubridæ* are divided into eight sub-families of which three are non poisonous three are mildly poisonous and two are highly poisonous and in the *Viperidæ* there are two sub-families all the species of which are poisonous

The sub-families of the *Colubridæ* and *Viperidæ* are sometimes grouped according to the nature and position of their fangs if these are absent, as in the three non poisonous sub-families of the *Colubridæ* the snakes are known as aglypha (γλ φα = a groove) if the fangs are behind the teeth they are known as opisthoglypha (οπισθεν = behind) if the fangs are developed from the front teeth and are grooved, they are known as proteroglypha (προτερος = before) and if the fangs are hollow tubes (like hypodermic syringe needles) they are known as solenoglypha (σωλην = tube) The first three of these groups correspond to non poisonous mildly poisonous and highly poisonous sub-families respectively of *Colubridæ* and the last to the *Viperidæ* The opisthoglypha snakes from the position of their fangs are incapable of injecting a fatal dose of venom into man but their bite is nevertheless poisonous and they kill small prey by this means.

The families and sub-families of the sub-order Ophidia with their main characteristics and commoner species are shown in table A (*a*) and (*b*)

IDENTIFICATION

The identification of the species of a snake is a highly technical procedure that is the domain of the zoologist or more especially the herpetologist it takes account of the characteristics of bones and teeth and of the arrangement of the scales as well as the general shape and size of the body However it is possible by the study of external characteristics alone for the less highly specialized observer to make a provisional identification. The characteristics to be studied are shown in table B

Poisonous or non poisonous?—For practical purposes it will usually be sufficient to distinguish between the poisonous and the non poisonous species of snakes

If the fangs and teeth are intact and can be examined, they pro the simplest means of answering the above question. The upper should be examined* to ascertain whether the snake is —

Aglyphous	Two rows of teeth on either side of the maxilla and no fangs	Non-poisonou
Opisthoglyphous	Two rows of teeth with one pair of grooved fangs at posterior end of outer row	Mildly poiso
Proteroglyphous	One row of teeth on either side with outer rows replaced by a pair of short rigid grooved fangs at anterior end with or without accessory fangs	Poisonous.
Solenoglyphous	One row of teeth with a pair of long tubular movable fangs and one or more pairs of accessory fangs	Poisonous.

Snakes can also be identified with a fair degree of certainty observing certain external characteristics and using the following sch and the figures on plate XXVI.

It is important to remember that colour is seldom of use as a dis guishing characteristic, the colour of most species is variable, to a gre or lesser degree. However plate XXV will give some idea of the u colour of some of the more common Indian poisonous snakes

TABLE A (a)

Showing main characteristics and habitats

Family	Examples	Habitat
1 *Typhlopidæ* (non-poisonous) Small worm-like burrowing snakes uniform small scales maxilla toothed mandible bare	*Typhlops braminus*	Tropical Asia including India Tropical Africa.
Tail small, usually as thick as the head end.	*T diardi*	India
Distribution—widespread in tropics Species—over 100	*T proximus*	Australia
2. *Leptotyphlopidæ* or *Glauconiidæ* (non-poisonous)	*Glauconia blanfordi*	India
Resembles the preceding family except maxilla bare. mandible toothed, tail long Distribution—cosmopolitan Species—over 30	*Leptotyphlops dulcis*	North America
3 *Aniliidæ* or *Ilysiidæ* (non poisonous) Burrowing snakes of variegated colour usually about 2½ to 3 feet	*Cylindrophis rufus*	South-east Asia
long claw-like spur at the vent representing vestigial remnants of	*C maculatus*	Ceylon
hind limbs ventral shields slightly enlarged. Species—6	*Ilysia scytale*	Tropical America

* Great care should be exercised in examining recently killed snakes, as muscu spasm may occur and many people have been bitten by a dead snake

TABLE A (a)—*concld*

Family	*Examples*	*Habitat*
4 *Boidæ* (non-poisonous) Includes several largest constricting serpents claw-like spurs at vent which is much longer than the preceding family very large number of scales on the dorsum of the body Ventral are moderately enlarged but do not stretch across abdomen		
Sub-family (i) *Pythoninæ* Supra-orbital bon present Premaxilla—toothed Species—over 20	*Python mol rus* (the rock python) *P reticulatus* (the royal python) *P spilotes* *Liasis fuscus*	South-east Asia India, Burma Malay Peninsula etc. Australia New Guinea North Australia.
(ii) *Boinæ* Supra-orbital bone present Premaxilla—bare Species—about 40	*Constrictor constrict r* (boa-constrictor)	Tropical America
	Eunectes murinus (anaconda)	Tropical South America
	Eryx conicus (so-called two-headed snake)	India
	E johnii (so-called two-headed snake)	India
5 *Uropeltidæ* (non-poisonous) Short bevelled tail usually covered with a scute variegated coloration of dorsal scales which are glossy and sometimes iridescent Ventrals moderately enlarged but do not stretch across abdomen Eye covered in the ocular shield except the genus *Platyplectrurus*. Found only in Southern India and Ceylon Burrowing habits, length 1 to 2 feet Species—about 50	*Uropeltis grandis*	Ceylon
	Rhynophis oxyrhynchus.	
	R sanguineus	South India
	Silybura grandis	"
	Plectrurus perroteti	"
	Platyplectrurus trilineatus.	"
6 *Xenopeltidæ* (non-poisonous) Contains single genus High iridescent uniform black or brown in colour Ventrals enlarged and almost cover the abdomen. Usually about 3 feet long Prema illa—toothed Species—1	*Xenopeltis unicolor*	South-eastern Asia South India.
Amblycephalidæ (non-poisonous) Lumpy head on a slender neck, large eyes pupils ertical Mental groov absent* Ventrals much enlarged stretching cross abdomen Slender body long t pering tail arboreal in habits. Species—about 40	*Amblycephalus monticola*	Eastern India, Burma

* Except for the absence of mental groove this family resembles in external characters the family *Colubridæ*, and for this reason some modern authorities classify it as a sub-family *Amblycephalinæ* f the family *Colubridæ*

TABLE A (b)

	Family	*Sub-family*	*Examples*	*Habitat*
8	*Colubridæ* Usually nine large scales or shields on the head (*see* figure 18) Ventrals usually much enlarged and stretch across abdomen except in sub-families (i), (iv) and (viii) Pupils usually circular	(i) *Acrochordinæ* (non-poisonous) Scales discrete, ventrals slightly or not enlarged Aquatic habits. Species—5	*Chersydrus granulatus*	Estuarine areas and coasts of South-eastern Asia, India, etc.
			Acrochordus javanicus	South-eastern Asia to Northern Australia.
		(ii) *Dasypeltinæ* (non-poisonous) Cervical vertebræ possess tooth-like processes projecting into œsophagus used to break birds' eggs, its only food. Species—1	*Dasypeltis scabra*	Africa
	A *Aglypha* No grooved teeth or poison glands.	(iii) *Colubrinæ* (non-poisonous) Great variety of size and form Habits different racers, arboreal or semi-aquatic cosmopolitan in distribution Species—over 700	*Ptyas mucosus* (the rat snake) *Lycodon aulicus* (the wolf snake) *Tropidonotus stolatus* (the grass snake) *Natrix piscator* (the pond snake) *Coluber helena* (the trinket snake) *Simotes arnensis* (the kukri snake) *Oligodon subgriseus* *Polydontophis sagittarius* *Dendrophis pictus* (the whip snake) *Dendrelaphis tristis*	India, Burma, Ceylon, South-eastern Asia.
			Coronella austriaca *Elaphe quatuor lineata.* *E æsculapii*	Europe and adjoining countries.
			Lampropeltis getulus (the king snake) *Elaphe guttata* *Pituophis sayi* *Coluber constrictor*	North America
			Coluber algirus *C florulentus*	Africa

TABLE A (*b*)—*contd.*

Family	*Sub-family*	*Examples*	*Habitat*
B *Opisthoglypha.* Small fangs at the back of the maxilla Small poison glands.	(iv) *Homalopsinae* (mildly poisonous) Ventrals slightly enlarged, do not stretch across abdomen River and estuarine snakes Tail slightly compressed in many species Species—about 25	*Cerberus rhyncops* *Hypsirhina enhydris* *H macleayi*	India, South-eastern Asia. India, South-eastern India Australia
	(v) *Elachistodontinae* (mildly poisonous) Like *Dasypeltis* so it possesses tooth-like projections into the oesophagus to break bird eggs. Species—1	*Elachistodon westermanni*	North Bengal
C *Proteroglypha.* Anterior maxillary teeth grooved (fangs) which are erect and small, connected with highly developed venom glands venom-neurotoxic	(vi) *Dipsadomorphinae* (mildly poisonous) A parallel to sub-family Colubrinae comprising racers, arboreals, and semi aquatics of various size and shape Species—about 300	*Dryophis mycterizans* (the green whip snake) *Chrysopelea ornata* *Dipsadomorphus trigonatus* (the cat snake) *D dendrophilus* *Dispholidus typus* (the boomslang) *Pseudoboa cloelia* Mussurana.	South-eastern Asia India Malay Peninsula South Africa Tropical America
	(vii) *Elapinae* (highly poisonous) Terrestrial, arboreal or semi-aquatic in habits. Tail cylindrical and tapering Ventrals very much enlarged and stretch across abdomen They are among the most deadly of all serpents. Species—about 180	*Naja naja* (the common cobra) *N hannah* (the king cobra) *N haje* (the Egyptian cobra or asp) *N nigricollis* (the spitting cobra) *N flava* (the cape cobra) *Bungarus candidus* (the common krait) *B fasciatus* (the banded krait) *Dendraspis angusticeps* (the mamba) *Pseudechis porphyriacus* (the black snake)	Tropical Asia including India South-eastern Asia North Africa Africa South Africa India India and South-eastern Asia. Africa Australia

TABLE A (*b*)—*contd*

Family	*Sub-family*	*Examples*	*Habitat*
C *Protero-glypha*—contd		*Notechis scutatus* (the tiger snake)	Australia
		Acanthophis antarcticus (the death adder)	"
		Denisonia superba (Australian copper head)	"
		Callophis macclellandi (the coral snake)	Eastern India, Southern China Burma.
		Micrurus fulvius (the harlequin snake)	North America
	(viii) *Hydrophinae* (highly poisonous) Sea snakes. *Tail flat oar-shaped* Ventrals either slightly or not enlarged. Nostrils open at the upper surface of snout. Species—over 50.	*Enhydrina valakadien* *Distira robusta* *Hydrus platurus*	Indian Ocean Tropical Pacific Ocean of Asia and Australia
		Pelamydrus platurus	Pacific Ocean along Tropical America.
9 *Viperidae* (highly poisonous) Usually triangular head distinct and differentiated from a thick body by a narrower neck tail short. Pupils vertically elliptical in most cases. Ventral scales very much enlarged, stretching across abdomen.	(i) *Viperinae* (highly poisonous) True or pitless vipers. No loreal pit head scales small except in the genus *Azemiops* Distribution—Asia Africa and Europe. Not found in America or Australia Species—about 50	*Daboia* (the Russell's viper)	India, Ceylon, Burma, Thailand.
		Echis carinatus ('Phoorsa')	North Africa South-western Asia, India
		Bitis arietans (the puff adder)	South-western Asia, Africa.
		B gabonica (the gaboon viper)	Africa
		B nasicornis (the rhinoceros viper)	
		Vipera berus (the adder)	Europe
		V aspis (the asp)	"
		Azemiops feae (the Fea's viper)	Burma, China

TABLE A (*b*)—*concld*

Family	*Sub-family*	*Examples*	*Habitat*
D *Soleno-glypha* Anterior maxillary teeth are canaliculated (fangs) very large, not always erect, can be folded under the palate, connected with large venom gland. The venom is hæmotoxic	(ii) *Crotalinæ* (highly poisonous) Rattlesnakes. A *loreal* pit present between the eye and the nose and rattles on the tail. Head scales small in crotalus; head shields in sistrurus. Distribution—America. Not found in Europe, Asia, Africa and Australia. Species—about 30	*Crotalus confluentus* (the rattlesnake)	North America
		C. adamanteus (Eastern diamond backed rattlesnake)	,,
		C. atrox (Western diamond-backed rattlesnake)	,,
		C. horridus (the banded rattlesnake)	,,
		C. terrificus (the dog faced rattlesnake)	,, ,,
		Sistrurus catenatus (the massasauga rattlesnake)	
		S. miliarius (the pigmy rattlesnake)	,,
	(iii) *Lachesinæ* (highly poisonous) A loreal pit but no rattles. Small head scales except the genus *Agkistrodon*. Distribution—America and Asia. Species—about 70	*Agkistrodon mokasen* (the copper head)	,,
		A. piscivorus (the water moccasin or cotton-mouth)	,,
		A. bilineatus (the tropical moccasin)	Central America
		Agkistrodon himalayanus (the Himalayan pit viper)	Himalaya
		A. hypnale (the Karawala)	Ceylon South India
		Bothrops atrox (*B. lanceolatus*) (the Fer-de-lance)	South and Central America, West Indies
		B. jararaca (the jararaca)	South America
		B. jararacussu (the Jararacussu)	
		Lachesis mutus (the bushmaster)	South and Central America
		Trimeresurus gramineus (the green pit viper)	India, South-eastern Asia, East Indies
		T. monticola (the large-spotted viper)	Eastern India, Burma, Southern China.
		T. flavoviridis (the Habu)	Eastern Asia

TABLE B

Data required for identifying the species of a snake from its external characters

(1) Size	(a) Length including the tail (b) Length of the tail only
(2) Shape or form	(a) Tail—whether flat or cylindrical tapering, slender or stumpy bevelled rounded or pointed rattles present or not (b) Body—whether stout moderate sized or slender (c) Head—whether distinct from the neck or not broad or narrow high or flat. (i) Snout—pointed or obtuse (ii) Nostrils—whether on the sides or on top of the snout and whether valved or open. (iii) Eyes—whether large moderate or small (iv) Pupils—whether round or elliptical (vertically or horizontally) (v) Loreal pit—between eyes and nostrils—present or not. (vi) Neck—whether distensible or not
(3) Coloration	Ground colour of the dorsum and ventrum any colour pattern such as longitudinal and transverse markings stripes or streaks, spots rings or other markings. Markings on the head and tail.
(4) Arrangement of scales or lepidosis	(a) Body and tail (i) Ventrals—whether broad moderate sized or narrow rigid or angulated at the sides their number (ii) Anal—whether divided or entire (iii) Sub-caudals—their number divided or entire. (iv) Dorsal—number of longitudinal rows in the mid-body character of the scale—whether discrete or imbricated smooth, tuberculated or keeled cycloid, oval or rhombic. (v) Vertebrals—whether enlarged or not, hexagonal or rhombic (b) Head (i) Whether shields or scales if shields—their pattern, shape and size (ii) Supra-labials—their number and pattern, especially the relation of the 3rd supra-labial in the family *Colubridæ*. (iii) Infra labials—their number and pattern. (iv) Sub-linguals—size and shape whether the mental groove is present.
(5) Arrangement and character of teeth	(i) Whether both maxillæ and mandibles are toothed. (ii) How many rows of teeth on the upper jaw (iii) Premaxilla toothed or not. (iv) Fangs present or not if present—whether anterior or posterior grooved or hollow tubes.

SNAKE BITE

Epidemiology.—The geographical distribution of snake-bite is naturally dependent on the geographical distribution of the dangerous species of venomous snakes this can be seen from the table above. India the East Indies tropical Africa and tropical America are the fields richest in snakes and India with at least 70 species of poisonous snakes heads the list.

On the other hand, there are many islands that are free from terrestrial poisonous snakes *e.g.* Iceland Ireland New Zealand Madagascar Hawaii and many islands in the South Pacific and several in the West Indies

In Europe there are few poisonous snakes the most common are the adder (*Vipera berus*) and the asp (*V aspis*)

In Australia the commonest causes of snake-bite death are the death adder (*Acanthophis antarcticus*) the tiger snake (*Notechis scutatus*) and the black snake (*Pseudechis porphyriacus*)

In Africa the commonest deadly snakes are the mamba (*Dendraspis angusticeps*) the spitting cobra (*Naia nigricollis*) the puff adder (*Bitis arietans*) the rhinoceros viper (*B nasicornis*) the asp (*Naia haje*) and the cape cobra (*Naia flava*)

In North America, poisonous snakes are relatively common in the mountainous and marshy districts The best known are the rattlesnakes the diamond backed rattlers (*Crotalus atrox* and *adamanteus*) the banded rattlesnake (*C horridus*) and the massasauga (*Sistrurus catenatus*) the rattleless pit vipers the water moccasin or cotton mouth (*Agkistrodon piscivorus*) and the copper head (*A mokasen*) and the harlequin (coral) snake (*Micrurus fulvius*)

In South and Central America the most feared snakes are the bush master (*Lachesis muta*) the Fer-de-lance (*Bothrops atrox*) and the jararaca (*B jararaca*) but there are many other species

In India, the cobras the kraits the Russell's viper and the echis viper are the snakes mainly responsible for the high mortality

In countries where poisonous snakes are abundant death from snake-bite constitutes not an unimportant cause of mortality Between 20,000 and 25 000 deaths from snake-bite are reported annually in British India Although snake-bite is sometimes a convenient euphemism for death by violence, in other instances death from snake-bite will escape registration as such, so that on the whole the figure probably represents something near the truth On the other hand, in Australia between 1910 and 1926 the average annual deaths from snake-bite numbered less than 15 For the rest of the world the annual deaths from snake-bite are usually placed at between 5,000 and 10,000

Few snakes are aggressive as far as man and other large mammals are concerned and the majority only bite when attacked frightened or accidentally injured. The persons most affected therefore are the bare-footed villagers walking along a jungle path at night who may accidentally tread on a snake Snakes will often come into a hut or house to escape unfavourable climatic conditions—cold, extreme heat or rain—and it is not uncommon for a person to be bitten when he or more frequently she places a hand into a receptacle in a dark corner

Children are frequently bitten either in and outside their huts and the bites are fatal in a much higher percentage of cases in children, as the toxicity is dependent on the proportion between the amount of venom injected and the body weight of the subject.

ANATOMY AND TOXICOLOGY

Poison apparatus.—This consists of a pair of poison glands connected by ducts to the grooved or canaliculated fangs on the maxillæ The poison glands are modified supra labial glands analogous to the parotid glands of the mammals They occupy an intermuscular space in the temporal regions below and behind the orbit on either side of the upper jaw (maxillæ)

The glands are enveloped by a fibrous capsule to which are partly attached the fibres of the masseter muscles, and are surrounded by a group of muscles consisting of the anterior middle and posterior temporal, and the digastric During the act of striking, these muscles are involuntarily contracted and the glands are violently squeezed so that the venom

is driven along the duct to the grooved or canaliculated fangs and thence to the tissues of the victim even if the snake misses its victim venom will sometimes be ejected The venom of the spitting cobra *Naia nigricollis* can be ejected a distance of 6 to 8 feet and it will cause temporary blindness if it comes in contact with the eyes In other species especially the *opisthoglyphæ*, the actual pressure of the bite appears to be necessary to eject the venom.

In the proteroglypha and solenoglypha the *fangs* which are situated anteriorly on the maxillæ differ one from the other in their structure, size and shape. In the proteroglypha (*Colubridæ*) the fangs though slightly movable are erect and small the groove which runs anteriorly lengthwise from the base to the tip of the fang is open, *but in the living state is* covered by a fold of mucous membrane which thus completes the canal. In the *solenoglypha* (*Viperidæ*), the maxillæ with large completely canaliculated fangs attached *to them* are movable and are controlled by various muscles In the resting position when these muscles are relaxed, the fangs are kept folded under the palate inside a sheath of mucous membrane (vagina dentis) but when the muscles are contracted for the strike or bite, the fangs come forward *automatically* and project at a right angle from the maxillæ this movement of the fangs does not take place in the proteroglypha. Besides the main fangs there are always reserve fangs behind, *in both* the viperine and poisonous colubrine snakes and these come into operation when the main *fangs are broken*

The venom. *Physical nature*—It is a colourless or golden-yellow liquid of thick consistency neutral or slightly acid with a specific gravity of from *1,030 to 1,060 or more. When* desiccated it yields about 25 to 50 per cent of solid matter and becomes a crystalloid substance which is soluble in normal saline.

It is thermolabile and destroyed by the gastric juice

Quantity—The venom is collected either by compressing the gland or by spontaneous bite of the snake on a parchment or rubber membrane spread over any convenient receptacle* The latter method gives a better *yield. The quantity* of venom varies with each species and with the size of the individual from about 8 mg. in the krait *to 375 mg. in the cobra.*

Chemical composition of the venom—The results of a broad analysis of the venoms of various poisonous snakes show that they consist of —

(1) *protein matter—albumin and globulin* (coagulable by heat)—which forms the major portion

(2) substances of the nature of proteoses and peptones (not coagulable by heat)

(3) *enzymes or ferments*

(4) inorganic salts (chlorides phosphates etc)

(5) a trace of fatty matter and

(6) *colouring matter*

Toxic principles—It was at one time generally believed that the coagulable proteins the non-coagulable protein like substances and the enzymes were responsible for the toxicity of the venoms but separate toxic elements of a non protein nature have been isolated *from* the protein molecule with which they are associated. The substance from cobra (*Naia naia*) venom has been called ophiotoxin ($C_{17}H_{26}O_{10}$) and from that of the rattlesnake, *Crotalus adamanteus* crotalotoxin ($C_{34}H_{54}O_{21}$) *It is* believed that these substances are of the nature of glucosides free from nitrogen and belonging to the saponin group

* In India, the snake charmers collect venom in the shell of a water mussel over which a palm *leaf* is tightly held. The snake bites on the palm *leaf and the poison* trickles down into the cavity of the shell

The toxicological action of the venoms of different species of venomous snakes varies widely and depends upon the summation of various toxic principles present in the venom the proportions vary with each species The toxic principles are —

(1) neurotoxins, with special affinity (*a*) for the nerve cells and particularly for the respiratory centre, and/or (*b*) for the nerve terminations of the muscles, especially for those of the diaphragm

(2) various cytolysins namely

(*a*) hæmolysin—acting on the red blood cells

(*b*) hæmorrhagin or endotheliolysin—acting on the endothelial cell lining the blood vessels and allowing the blood to extravasate

(*c*) cytolysins acting on cells of several other tissues such as the liver kidneys etc

(3) an antifibrin ferment (protease) destroying the fibrinogen thus acting as an anti-coagulin

(4) a fibrin ferment (thrombase) causing thrombosis

(5) a proteolytic ferment and

(6) a cardiac toxin, which in small quantities tones up the heart, but in higher concentration stops it in systole

Selective action of different venoms.—As a general rule, the venoms of *Colubridæ* contain a predominating quantity of neurotoxins this is especially true of the common cobra the krait the tiger snake the black snake, the death adder and the sea snake In the cobra venom neurotoxins are responsible for 60 per cent of its toxicity hæmolysins and anti coagulins for about 40 per cent, and a proteolytic ferment for the rest

On the other hand in the *Viperidæ* the venom, as a rule contains a high proportion of hæmorrhagin Thus in the Russell's viper venom hæmorrhagin represents about 70 to 75 per cent of the total toxicity the cytolysins, thrombase and cardiac toxin represent about 20 to 25 per cent, and the proteolytic enzyme the balance. But there are exceptions to this rule as in *Crotalus terrificus* a viper the venom is strongly neurotoxic

Minimal lethal dose of different venoms for man.—Acton and Knowles (1921) estimated the minimal lethal dose (MLD) of cobra venom for man to be 15 mg. by a study of fatal cases of cobra bite given in the literature in which no treatment or valueless treatment had been administered. The MLD for the venoms of other Indian species of poisonous snakes was also calculated by them on the assumption that the relative toxicities of different venoms for the monkey hold good for man.

The data in the following table were taken from their papers and from other sources

Snake	Approximate dose given at bite mg.	Estimated fatal dose for man, mg
Naia naia	211 3	150
Naia hannah	100 0	120
Bungarus candidus	5 4	1 0
B fasciatus	42 9	10 0
Daboia russellii	72 0	42 0
Echis carinatus	13 3	5 0
Lachesis gramineus	14 1	100 0
A mokasen	45–60	Approximately 25 0
A piscivorus	90–150	
C horridus	60–90	
(ad manteus	40–450	
B t or	60–160	
La hesis m ta	300–500	
D angusticeps (mamba)	60–60	

hysteria, but the object symptoms such as cyanosis and hæmorrhages will of course be absent. On the other hand the symptoms of a child whom it is usually possible to reassure, can be taken at their face value.

More help will be obtained from the local signs there will be only very slight redness or swelling, the characteristic paired fang marks will be absent, teeth marks will be superficial, and there will be no bleeding from them also there will be no local loss of sensation, nor paralysis but these may be simulated by a hysterical patient.

Differentiation between colubrine and viperine poisoning.—This also is difficult in the early stages when the differentiation may be of any value. In colubrine poisoning local pain passes fairly rapidly and is replaced by local anæsthesia local paralysis develops and there is some local œdema. In viperine poisoning local pain is marked and persistent there is a more intense local reaction which may include echymosis around the puncture, and there will be no local paralysis. In the later stages, more marked differences in the general symptoms appear (*vide supra*) Shortly the predominant symptoms in the former are paralytic, and in the latter hæmorrhagic

PROGNOSIS

This is dependent on a large number of factors, several of which are unappraisable and it must therefore be very guarded. (It is however essential that the patient himself must be reassured for his own sake)

The *factors concerned* are —

(*a*) The species of the snake and the individual variation in the toxicity of its venom (*b*) the amount of venom injected, (*c*) the site of the bite, (*d*) the body weight of the victim (*e*) the immediate measures adopted, and (*f*) the facilities available for treatment.

(*a*) If the snake is not identified this factor can only be gauged in general terms for example the snakes of Europe Australia, and temperate countries generally are much less poisonous than those of India and other tropical countries

(*b*) The amount of venom injected is dependent on the efficacy of the bite which will to some extent depend on (*c*) the part bitten a bite on a small member such as a finger or toe or even hand or foot, is likely to be more effective as for mechanical reasons, the poisoning mechanism can come into full play on the other hand, in such a position it will be easier to give effective local treatment.

(*d*) The body weight is important, as the effect of a given amount of poison will be in inverse ratio to the body weight therefore, the larger the individual the better are his chances of recovery

(*e*) The prompter the application of the ligatures and other immediate measures the better the prognosis.

(*f*) Finally to be of any use specific or polyvalent serum must not only be immediately available but available in sufficient amount.

TREATMENT

Introduction.—More fables have grown up around the treatment of snake-bite than around any other procedure in medical practice. Many millions of inhabitants of eastern countries are firm believers in amulets snake-stones potions with a most diverse range of ingredients—from plant juices to powdered gallstones—and/or prayers and incantations, as infallible cures for snake-bite. This credulity is not confined to the uneducated classes nor even to the inhabitants of eastern countries for there is a widespread belief amongst the laity of western countries—a belief

at is even accorded semi-official recognition in countries where prohibi on is in force—that the drinking of a bottle of whisky is the best eatment for snake-bite This is not difficult to understand for it is not ually appreciated that the large majority of snakes are non poisonous nd that even poisonous species often fail to inject a fatal dose, so that l remedies however useless will enjoy at least a ten-to-one chance in vour of success and with a run of luck may easily acquire a reputation or infallibility

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NON-SPECIFIC PROCEDURES

(a) Localization of the venom (i) *Tourniqute*—The application f some form of tourniquet, either a tightly applied one to prevent arterial ow or a lightly applied one to cause venous congestion and control lymph eturn appears to be the commonsense procedure, but nevertheless it is ot a measure that is universally recommended. The main cause against he tourniquet is that no tourniquet will prevent the poison spreading hrough the tissues and an arterial tourniquet at least will often do considerable and unnecessary local damage. On the other hand, most ractical workers consider that a lightly applied tourniquet is always beneficial and some recommend an arterial tourniquet as well. The writers elieve that combined with other measures at least a light ligature should be applied and one of us (S. K. G) has seen marked benefit from an rterial ligature in preventing the neurotoxin reaching the central nervous system in colubrine-bites.

(ii) *Refrigeration*.—There is little practical support for this theoretically plausible procedure but it is sometimes worth practising if only for its psychological effect.

(b) Elimination of the venom at the site.—(i) *Multiple incisions* should be made with aseptic precautions and if possible under local anæsthesia, a large deep (¼ to ½ inch according to the depth of the bite) crucial incision through the fang marks and a series of small (¼ inch by ¼ inch) incisions around the edge of the advancing swelling blood vessels must be avoided and if cut, tied.

(ii) *Suction* may be effected by means of Bier's suction tubes a breast pump, or some special suction apparatus such as that suggested by Jackson (1929) Suction by applying the mouth to the wound should be looked upon as a first aid measure. Suction must be combined with ligature and saline irrigation, and continued for a long time Although much of the toxin is absorbed by the local tissues a considerable amount can be extracted by this means as experience has shown that the extracted fluid is very toxic.

(iii) The objects of *excision* and *amputation* are the same namely the removal of the tissues in which the toxin is fixed. The choice of procedure will depend on the site of the bite and amputation should only be considered in the case of bites on the toes or fingers These measures should only be undertaken when the limb has been effectively ligatured continuously since the bite or when it is possible to excise the site or amputate the limb immediately after the bite.

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that is even accorded semi-official recognition in countries where prohibition is in force—that the drinking of a bottle of whisky is the best treatment for snake-bite. This is not difficult to understand for it is not usually appreciated that the large majority of snakes are non poisonous and that even poisonous species often fail to inject a fatal dose, so that all remedies however useless will enjoy at least a ten to-one chance in favour of success, and with a run of luck may easily acquire a reputation for infallibility.

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(c) Neutralization of the venom *in situ*.—Local infiltration with calcium hypochlorite, potassium permanganate gold chloride or other substances some of a secret nature has been advocated in the past and is still considered by some workers to be a valuable procedure However the present trend of opinion is against any local injection except with antivenene. The latter if available, should always be used, at least in the case of viper bite and as much as they will take should be infiltrated into the tissues around the bite

(d) Treatment of general symptoms. (i) *Primary shock*.—The patient should be laid on his back with his head slightly lower than his feet he should be given hot coffee or tea, and reassured and calmed. Caffeine may be given as a stimulant and morphia ¼ grain if there is severe pain Alcohol should not be given unless it is obvious that the bite was a non poisonous one in such a case, given in moderate amounts, it will help to combat primary shock from fear

(ii) *Secondary shock and collapse*—Hæmorrhages and vasomotor failure may lead to collapse which should be combated by the usual procedures including plasma or serum transfusions of at least two pints, and pituitrin and adrenalin. In the absence of plasma whole blood may be used. Chopra and Chowhan (1939) strongly advocate veritol (15 to 30 mg. intramuscularly or 40 to 80 mg. by mouth)

(iii) *Hæmorrhages*—For the multiple hæmorrhages after viperine-bite injections of calcium chloride or gluconate, congo-red solution, vitamin C vitamin K and hæmostatic serum have all been advocated and each appears to have been of value in certain cases

(iv) *Respiratory paralysis* caused by the neurotoxins may occur Respiratory stimulants such as coramine and cardiazol by the parenteral route may help to alleviate respiratory embarrassment but in some cases artificial respiration and oxygen may have to be maintained for several hours.

(e) Treatment of complications and sequelæ (i) *Sepsis*—Septic absorption from the site after viperine-bite is not uncommon. Early administration of drugs of the sulphonamide group prevents this complication. Some authorities advocate the routine use of antitetanic serum in prophylactic doses.

(ii) *Gangrene*—It frequently occurs after viperine-bite and is due to the action of thrombase Early administration of antivenene, early release of the ligatures and when the general symptoms appear to be well controlled vigorous local treatment with frequent hot fomentations will usually prevent gangrene but once it supervenes amputation is the only remedy

(iii) *Other complications and sequelæ*—*Hæmopericardium hæmothorax hæmarthrosis, pyæmia* and *nephritis* are some of the sequelæ of viperine-bite each of these requires its own line of treatment

SPECIFIC TREATMENT

Antivenene.—The only specific treatment against poisonous snake-bites is the early administration by the intravenous route of antivenom serum, so-called antivenene. As the venoms of different species of snakes differ in their toxic principles different antibodies are produced in the immunized animal (horse) and the antiserum produced against the venom of a particular species is effective against that venom alone or against the venom of closely related species. For example in India antivenene either against cobra venom or Russell's viper venom (the two commonest poisonous species which are responsible for the majority of the 20,000 or more annual snake-bite deaths) will not protect the victim bitten by the

other species. To surmount this difficulty polyvalent sera which are effective against more than one common local species have been prepared by serum institutes of different countries. Heterologous serum is sometimes used but there is little evidence that it is of any real value

Dosage.—The points to be considered in calculating antivenene dosage are —

(a) The amount of venom inoculated this is an unknown quantity but the average quantity injected by a snake of the particular species is usually known (see table on p 807) and some idea of the efficacy of the bite may be obtained from the site and the circumstances of the bite.

(b) The toxic activity of the venom of the individual snake this is always an unknown quantity but is likely to vary from country to country and the venom is usually more toxic in tropical countries

(c) The neutralising capacity of the antivenene for example whether it is concentrated or not 1 c.cm. of polyvalent antivenene (Kasauli) given intravenously will neutralize 0 4 mg of dried cobra venom or 0 9 mg of Daboia venom.

(d) The time that has elapsed after the bite.

(e) The route of administration the intravenous route is three to four times more effective than the intramuscular or subcutaneous

It will be seen from the above and from the table on p 807 that the amount of concentrated polyvalent antivenene for intravenous injection required in the treatment of an average cobra bite will be 130 c.cm and of an average Daboia bite 23 c.cm. in practice, however it is usually advisable to give not less than 40 c.cm. in the latter case. The subcutaneous route is of little value because of the slow rate of absorption but it should be remembered that such large doses of horse-serum given by the intravenous route may cause severe anaphylactic symptoms in susceptible individuals

Precautions.—In the case of persons giving a history of allergy such as asthma or hay fever or of previous injection of horse-serum, a test for sensitiveness to the proteins of horse-serum must be made by giving

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In India, the Central Research Institute Kasauli (Punjab) prepares and issues in 10 c.cm ampoules concentrated (high titre) polyvalent antivenene which is effective against both cobra and Russell's viper venom The serum is concentrated four times by the ammonium sulphate method, so that 10 c.cm. equals 40 c.cm. of unconcentrated serum of former times. It is available from the Director of the Institute at a cost of about four rupees per ampoule

Polyvalent high titre antivenene against two or more different local species are being produced —

(a) Butantan Institute in Sao Paulo, Brazil South America prepares four polyvalent antivenenes against (i) rattlesnakes, (ii) Bothrops, (iii) rattlesnakes and Bothrops, and (iv) coral snakes

(b) The South Africa Institute of Medical Research at Johannesburg, South Africa, prepares a polyvalent antivenene against the cape cobra the mamba and several species of African viper

(c) The Pasteur Institut of Lill France used to prepare a number of antivenenes against different species.

(d) Institute of Infectious Diseases of Tokyo Japan, used to prepare an antivenene against the habu *Trimeresurus flavoviridis*

(e) Public Health Department of New South Wales Australia, prepares an antivenene against Australian species

(f) In the United States M lford Laboratories prepare n ntic cratolule antiserum against North American Crotalinae (pit vipers) and Bothrops antiserum against Central and South American Lachesinae

The sera are usually issued in ampoules containing 10 c.cm. of serum which have to be kept in a cool place or they lose their potency It is probabl that the lyophile' process, in which the sera are frozen and dried to a powder will be applied to antivenene in the future and this will obviate the necessity of keeping them in a refrigerator

intradermally 0 1 c cm of a 1 in 10 dilution of horse-serum. If no skin reaction occurs the treatment may be commenced immediately In the case of a positive reaction (manifested by the appearance of an urticarial weal at the site of the injection which enlarges rapidly and is surrounded by a zone of erythema within 5 to 20 minutes) it is *absolutely essential* to desensitize the patient before giving the main dose.

The patient can be desensitized by the method described by Kellaway and Morgan (1931) The *following* doses are given at half hourly intervals, 0 025 c.cm. 0 1 c cm. and 1 0 c.cm. subcutaneously and finally 0 1 c.cm. intravenously If this dose causes no general allergic symptoms, the intravenous injection may be given very slowly If allergic symptoms occur, the injection should at once be stopped and 1/50th grain of atropin and 0 5 c cm. of a 1 in 1 000 solution of adrenalin chloride should be administered hypodermically

We have usually adopted the practice of giving 50 c cm. of concentrated antivenene intravenously diluted with the same quantity of 25 per cent glucose solution to start with and then the balance of the dose slowly in a pint of 5 per cent glucose in normal saline. No ill effects were noticed in any of the patients.

After the requisite quantity of antivenene has been given the ligatures may be removed.

PRACTICAL CONSIDERATIONS

When a patient is brought to him the first problems facing the practitioner will be to decide (*i*) whether the patient was *actually bitten* at all, (*ii*) whether or not the snake was a poisonous one, and in the former case (*iii*) whether it inoculated a fatal or dangerous dose. He then has to decide how far he is justified in carrying out possibly mutilating procedures on the chance that the snake may have been a *poisonous* one and that the dose may have been one that would ordinarily prove fatal.

If the snake is captured or killed and is not too badly mutilated, it must be identified (*vide supra*) A careful examination for tooth and/or *fang marks of the part supposed to* have been bitten and of the surrounding tissues for local reaction must be made.

Prompt action is necessary as delay may be fatal. The chances must be weighed on the evidence available (*see* Diagnosis) One's decision will naturally be somewhat influenced by the circumstances under which treatment is to be given for example, if there were a chance that the snake was poisonous it would be wrong to withhold antivenene, on the other hand one would hesitate to take such drastic procedures as amputating a limb or even making extensive incisions which might damage important *structures* and would usually be a potential source of sepsis, unless the suspicion were well founded.

It will be as well now to consider the case of snake-bite as an emergency in four different sets of circumstances.

A. In the jungle or bush where no medical equipment is available and first aid has to be applied.

B *In the isolated* village dispensary where no antivenene is obtainable.

C In an out-station hospital where although there is no antivenene at *hand this will be obtainable* within a few hours.

D In a well equipped hospital where antivenene is available in sufficient quantity

A *In the jungle or bush where no medical equipment is available. and first aid has to be applied.*—A ligature must be placed immediately above the bite and a second tight (arterial) ligature around the first

single-bone portion of the limb proximal to the first ligature that is except in the case of a bite on the tip of a digit when the second ligature might be put around the proximal phalanx around the humerus or femur Mouth suction should be applied over the punctures, and if a sharp and reasonably clean knife is available a crucial incision may be made into the fang marks to facilitate effective suction but it is doubtful if any further cutting procedures should be undertaken in these circumstances The patient must be reassured as far as possible and when they are available, given hot coffee or tea to drink and ¼ grain of morphia subcutaneously He must then be removed to the nearest place where further treatment can be given

Wherever possible the snake should be killed, without damaging the head unduly and identified or preserved for identification

Do not give alcohol if it is thought that the bite was by a poisonous snake as it is definitely detrimental.

B In the isolated village dispensary where no antivenene is obtainable —This is the situation that probably nine times out of ten faces the medical man who has to treat snake-bite in tropical countries A firm ligature sufficient to stop the lymph flow and the venous return, should be applied immediately proximal to the bite and an artery-occluding tourniquet further proximally around the upper arm or thigh. The patient should be assured and any treatment for primary shock thought necessary should be administered but alcohol should not be given (*vide supra*) The patient and his friends should be questioned more closely regarding the incident and a decision made as to the probabilities of the snake having been a poisonous one. This will be facilitated if the snake was killed and brought with the patient. If the decision is in favour of an effective bite by a poisonous snake then under a local or a general anæsthetic a series of incisions should be made under strict antiseptic conditions one deep crucial incision immediately over the bite a number of shallower (¼ inch) crucial incisions in a circle around the bite at the edge of the swelling, and, if the swollen area is a wide one several incisions should be made within this area. Suction must be applied for half an hour or more and as much fluid as possible drained away from the site The wound should be irrigated with warm citrate saline to encourage the bleeding. When the bleeding has stopped, the arterial tourniquet should be released and the suction repeated. The arterial tourniquet need only be reapplied if the bleeding is dangerously profuse The suction should be applied at hourly intervals for 10 to 15 hours but may then be discontinued if no further general symptoms appear, and any symptoms that have developed show evidence of subsiding. Plenty of fluid, including hot demulcent drinks must be given to the patient, and if during this procedure he loses a dangerous amount of blood a blood transfusion must be administered.

Other treatment for secondary shock and other general symptoms and for the various complications that may arise will naturally be given (*vide supra*)

C. In an out-station hospital where although there is no antivenene at hand this will be obtainable within a few hours —Tourniquets must be applied and vigorous local measures for eliminating the toxin as indicated above undertaken to prevent the absorption of a fatal amount before the antivenene is obtained. Primary shock must be treated and other symptomatic treatment applied as necessity arises

D In a well-equipped hospital where antivenene is available in sufficient quantity —If no tourniquet has been applied, both tourniquets and ice should be applied immediately while the patient or his friends are being questioned, and the syringe and antivenene are being prepared

for injection. Primary shock should be treated Then antivenene should be given, intravenously by preference, with the usual precautions (*vide supra*) If there is any question regarding the identity of the snake or when other than genus-specific antivenene is being given e.g in the case of echis- or krait bite when only the divalent cobra and Russell's viper antivenene is available local treatment for eliminating the venom must be undertaken (*vide supra*)

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SOME COMMON SKIN DISEASES OF THE TROPICS

TOKELAU or TINEA IMBRICATA

PITYRIASIS (TINEA) VERSICOLOR

LEUCODERMA or VITILIGO

Introduction—*There are few true* skin diseases that are confined* entirely to the tropics but several are undoubtedly more common more severe and acquire a special significance in tropical climates. It is to some of the more important of these that this chapter is devoted Every white sojourner in the tropics will know prickly heat, dhobie itch and *ringworm of the feet*—*by these or some other names*—as actual afflictions or ever present dangers. Pityriasis versicolor, which is a widespread infection amongst natives of the tropics and leucoderma which is a common enough condition in the tropics to justify its inclusion here are

* What does and what does not constitute a skin disease is a question that has yet to be answered satisfactorily Skin manifestations of specific systemic diseases should certainly be excluded, and the right of the ulcerative conditions to be included in this category seems equally doubtful neither of these groups is considered here On the other hand many skin diseases have a constitutional origin. Leucoderma is almost certainly an example of the latter

more important from an æsthetic than from a morbidity point of view but should be recognized as they may well be confused with other more serious conditions. Finally tinea imbricata is perhaps the only skin disease that has an exclusively tropical distribution

These conditions will be discussed mainly from the clinical point of view

PRICKLY HEAT

Prickly heat is probably the commonest of all syndromes suffered by the newly-arrived white man in the tropics and history has recorded that no less august personages than British governors-general in India have been observed rolling on the floor in the agonies of prickly heat during the monsoon in Bengal and yet our knowledge of the exact ætiology the pathology and the treatment is still far from complete

Epidemiology —It occurs in all tropical and in many sub-tropical countries but is especially associated with the green tropics and with the periods of year when humidity is high *e g* the monsoon in India

The dark skinned native of the tropics rarely suffers from this condition It is far more common in the newly arrived sojourner than in the older residents but the white man seldom becomes completely immune A degree of immunity is undoubtedly acquired but the main reason for the relative freedom from prickly heat enjoyed by the older resident is certainly that experience has taught him how to behave in the tropics and how to take simple precautions to avoid this distressing complaint. It is more severe in infants and children than in adults in men than in women in the thick-set than in the spare individual in the fair than in the dark, and is most pronounced in the obese.

It was more common in the past when the British soldier in India wore heavy broadcloth when the sojourner wore the formal dress of his country of origin, and when the cholera belt was considered an essential precaution, than it is to-day when the dress of both the soldier and the civilian sojourner is more rational It occurs more commonly amongst those persons whose circumstances prevent regular bathing and changing of clothes

Anatomical distribution —It occurs on parts of the body (*a*) where the clothes are held in close contact by pressure *e g* around the waist under the belt, on the shoulders where the weight of the clothes is taken and across the shoulder blades (*b*) where there is friction from clothes *e g* in the groin axilla and the backs of the wrists (*c*) where two skin surfaces are in continuous contact *e g* under the breasts and between the folds of fat in the obese and (*d*) on the backs of the hands a site where the frequent presence of prickly heat cannot be explained on any of the above grounds

Ætiology and pathology —On the subject of the ætiology of prickly heat there are several schools of thought

Smith (1927) claimed to ha e isolated a yeast-like fungus, apparently a monilia, regularly from the skin in this condition, but most other workers question the specificity of this organism There seems little reason to believ that the cutaneous moniliasis that he produced experimentally is identical with prickly heat the former is readil cured by 2 per cent gentian violet, which is certainly not true of the latter Blomfield (1943) appears to consider that prickly heat is due to functional failure of the sweat glands as a result of o eraction.

There is little doubt that infection plays an important part as there is always at least a mild inflammatory reaction, and all successful treatments have as part of their objective the removal of accumulated micro-organisms from the clothes and skin by frequent washings and their destruction by the use of mild antiseptics. In favour of the specific micro-organismal theory is the fact that some immunity

more than two minutes, so that after this interval it must be sponged off 15 minutes is usually the time recommended, but in the case of the less sensitive it is unnecessary to wash off the soap at all. 'Asepso', afridol and neko soap are to be recommended, the two former being the better

As an alternative to the antiseptic soap and to be applied at other times is a lotion of 1 in 2 000 perchloride of mercury in 90 per cent alcohol to be wiped over the affected part after it has been dried and itself allowed to dry (This will not suit all skins) Then a dusting powder consisting of camphor—20 parts, menthol—5 parts, boric acid—200 parts, zinc oxide—300 parts made up to 1 000 parts with fine talcum powder, should be applied.

As an alternative to the mercury spirit lotion and powder a white lotion made up of zinc oxide 20 per cent, menthol 1 per cent, camphor 2 per cent in 80 per cent alcohol should be dabbed on the affected area with a piece of cotton wool It is usually inadvisable to apply this more than twice during the day at other times an aqueous calamine lotion with phenol will be soothing

As in the case of most skin disease there is greater danger from over than under treatment and whenever any treatment appears to be irritating the skin, it must be discontinued and simple aqueous calamine lotion applied.

The sulphonamides have no effect on uncomplicated prickly heat, but, for the complications in which pyogenic organisms play a part sulphathiazole and sulphadiazine will be of considerable value

Prognosis.—This will depend on the personal factor on the opportunities for applying the measures recommended and on the vigour and wisdom with which they are applied. Seldom if ever, should it be necessary to invalid patients for uncomplicated prickly heat, but when they persistently develop multiple boils a short period of leave in a cool climate often appears to be the only way to cure this serious complication.

RINGWORM OF THE FEET TINEA PEDIS or DERMATOPHYTOSIS

This is a world wide condition but always assumes a much greater importance in the tropics and particularly in the humid tropics. In temperate climates, where it is usually known as athlete's foot, it often appears in epidemic form in schools and amongst athletic groups whose members transmit the infection to one another in dormitories, changing rooms and swimming baths, by walking barefooted, and by the communal use of bath slippers, sandals and towels. In the tropics where it has innumerable synonyms e g Hong Kong Singapore Bengal, etc foot-rot (indicating its geographic distribution) mango toe etc it is endemic, and where there are native servants walking barefooted, it is practically impossible to avoid infection, even by taking the most rigid precautions.

Epidemiology —This disease is at its worst under conditions of high temperature and high humidity In chronic sufferers it will often improve if not apparently clear up during the cool dry season, in those places where there is one or when the subject goes to a cool climate, but it returns in full force when the temperature or humidity rises again. It is more common in towns (hot pavements) than in country districts, amongst men than amongst women and amongst those who have to do a considerable amount of walking during the day (e g brokers) than amongst those whose occupation is mainly sedentary (e g bankers) The barefooted are usually infected but the infection is seldom active and in any particular set

of circumstances the activity of the condition will usually be in inverse ratio to the ventilating properties of the footwear

Ætiology and pathology—The causal organism is a fungus usually a species of *Trichophyton* but *Epidermophyton floccosum* and even the monilia, *Candida albicans* may be responsible the spores of these fungi are highly resistant and survive on wooden floors coir or grass mats carpets towels shoes etc., almost indefinitely despite vigorous treatment with strong antiseptics They are destroyed by autoclaving.

These fungi penetrate the epidermis and the superficial layers of the corium only, and their toxins cause a serous exudate to accumulate under the epidermis which is thus separated from its source of nutrition and dies

Symptomatology—The primary site of the infection is often between the fourth and fifth toes it soon spreads to the other interdigital spaces to the soles to the dorsum of the feet and particularly of the great toe, to the sides of the feet, to the soft area of skin between the ankle and the Achilles tendon and to the nail beds The same infection may also spread to other parts of the body (*vide infra*)

Small vesicles appear they are usually surrounded by a halo of inflammation. They are extremely irritating. After a few days the whole areas between the toes become white and pieces of sodden epithelium separate exposing the red corium covered by a thin transparent layer of epidermis, which tends to crack, bleeds if damaged by scratching and readily becomes infected with pyogenic micro-organisms After such infection has subsided, the epidermis gradually resumes its normal thickness, but soon becomes sodden and separates again. Meanwhile areas of hyperkeratosis develop at the margins of these lesions and form ridges along the edges of the dorsum of the toes and up the interdigital sulci on to the dorsum of the feet The infection will usually spread on to the soles especially to the parts under the arch where the skin is thinnest here the vesicles in the comparatively thicker epidermis cause intolerable itching, and develop to the size of a sixpence (¾ inch) or more. These blebs contain a clear fluid at first, but they often develop into pustules surrounded by areas of inflammation. Here too the epidermis may separate in large plaques but it usually flakes off the denuded skin tends to crack, and secondary infection and extensive cellulitis may result.

Complications—The danger of serious cellulitis is very real but there is another development that provides a good reason for not neglecting these infections, namely the occasional development of ids trichophytids or dermatophytids on the other hand it is believed that these sometimes develop as a result of too active treatment These ids are apparently an allergic manifestation which result from the patient developing a sensitivity to the mycotic toxins that have reached the general circulation from the local lesions. They take the form of severe erythematous rashes or papular vesicular or pustular eruptions on any part of the body but characteristically on the soles or palms the site bears no relation to the initial lesion except that in foot infections the ids very commonly appear on the palms producing a condition known as cheiropompholyx. This is a very distressing condition that completely incapacitates the sufferer for a period of seldom less than six weeks and often for much longer The whole of the skin of the palms separates and secondary infection in some degree is almost inevitable There may be two or three relapses before the condition finally subsides

Diagnosis—A clinical diagnosis is usually sufficient for practical purposes. However it is very easy to confirm that the lesions are due to a fungus infection by taking a scraping from the margin or removing

Symptomatology —The two main areas in which this co develops are (*a*) the inner aspects of the thighs, where radiating fr crutch it passes backwards to the perineum, on to the scrotum, ar the anal cleft, and (*b*) the axillæ where it spreads out on the aspects of the chest and on the under and inner sides of the arm former site is by far the commoner The condition is usually bilat

A red rough scaling area with a raised spreading papular and pustular margin develops, the lesion spreads fan wise. It is intol irritating and thus causes *continuous and involuntary scratching* c the sleep, which allows secondary infection to occur and increases i mation. The inflammation may be so severe that the patient can sc bear to put on his clothes and can walk only with great difficulty

Diagnosis.—This can be confirmed by taking scrapings fro margins of the lesions and macerating them in 20 per cent pot hydroxide, as in the case of tinea pedis

Prevention.—This condition is not nearly so difficult to prev tinea pedis. A good supply of cotton or linen pants and vests sho made available. After removal, these should always be washed wit in hot water rinsed out in clean water and dried thoroughly before put on again. If possible, this washing should be done personall most cases it will be left to the native servant, but care should be that he is himself not suffering from the condition, if he is, arrange should be made for his thorough treatment. The precautions to be are in fact much the same as those against prickly heat (*q v*) Aft bath, the susceptible areas should be carefully dried and powdered talcum powder

Treatment.—Before treatment is undertaken precautions again infection must be organized. The cotton pants and vests should be that they cover the whole affected area, that is to say in the case *axillary infection, vests with at least short sleeves must be used.*

Though the danger of over treatment does exist, it is usually l this condition than in tinea pedis, one reason being that the area more sensitive and the immediate pain of strong applications will pr their over use When however the areas are actually inflamed s fungicidal substances must not be applied until the inflammation has reduced by hot applications alternating with aqueous calamine lotion

Individuals with a tough *skin e.g negroes* and some Indians o labouring class, will usually stand strong applications, such as *for* (commercial) and liniment of iodine but even in these individuals must be exercised, and the doctor should himself apply the medicam and not leave this to the patient.

Perhaps the most useful preparation of all is Whitfield's ointmen

Salicylic acid	gr xxx
Benzoic acid	gr lx
Lanoline	½ ounce.
Vaseline	*to one ounce*

This is too strong for many skins and for the first application h strength Whitfield's ointment should be used. Later it may be pos to use the full-strength ointment, but the patient must be warned to continue the application if there is a severe inflammatory reaction. should also be warned to apply it to the scrotum very cautiously a may be exceedingly painful.

Alternative applications are 4 per cent gentian violet in 10 per cent alcohol or triple-dye There are also several proprietary preparations e g cignolin—a synthetic chrysarobin preparation—in the form of an ointment or a paint (1 to 3 grains in one ounce of pure acetone) which are useful

These fungicidal applications should be made daily after the morning bath care being taken that the area is first thoroughly dried In the case of half-strength Whitfield s ointment a second application may be made at night if there is no inflammatory reaction

A few days of conscientious treatment with any of these applications will usually cure this condition but the treatment must be continued for some time after symptoms have disappeared Refractory cases will occasionally be encountered in which a succession of medicaments may have to be tried

TOKELAU or TINEA IMBRICATA

This infection appears to have a purely tropical distribution It has been described in India Ceylon Burma Indo-China Malaya the Dutch East Indies Borneo New Guinea the South Pacific islands and China There are apparently a few foci of infection in Central Africa and in Brazil In India it is encountered almost solely amongst aborigines in South India Bengal and Assam and in a few plain folk who have been in close contact with aborigines

Ætiology.—The causal organism is *Trichophyton concentricum* (plate XXVII figure 2) This micro-organism differs from others of this group by its apparent inability to survive saprophytically for any length of time so that it can only be transmitted by direct contact It penetrates the epidermis between the epidermis and the dermis it multiplies abundantly causing the former to separate and in due course it penetrates the newly formed epidermis and causes further separation

Symptomatology—The lesion starts as a round or oval macule in the centre of which the horny layer of the epithelium cracks and flakes of epithelium begin to separate from within outwards. The lesion extends and a larger and larger ring of separating white scales is produced Meanwhile the area in the centre recovers to some extent its normal appearance but it soon cracks again and a new ring forms within the previous one so that the lesion eventually consists of a series of concentrically arranged brown (normal skin) and white (separating scales) rings these meet other similar groups of rings so that the whole skin area presents a most striking appearance suggestive of tattooing (plate XXVII figure 1) At the periphery of the individual lesion the horny layer becomes slightly thickened and raised but there is little inflammatory reaction

The lesions are very irritating

Extensive areas of the skin of the trunk and limbs are involved but the hair is not affected The head palms soles axillæ and groin are seldom affected

Diagnosis—Clinical diagnosis is usually easy on account of the unique appearance of the earlier lesions Old lesions with dark thickened edges will sometimes simulate ichthyosis but in such cases other fresh lesions will usually be found somewhere on the body

Prevention and treatment.—Personal cleanliness is an effective preventive measure The disease is said not to occur among persons who anoint their bodies with coconut oil

The lesions themselves respond fairly readily to treatment but the area involved is so extensive that the whole surface cannot be treated at

one time with any of the stronger fungicides. An additional complication is the fact that the patients are mostly uneducated aborigines.

Most fungicides are effective. Castellani's fuchsin paint* is usually recommended. Dey and Maplestone (1942), who have had considerable experience with this infection, recommend a paint of one drachm each of resorcinol and glacial acetic acid in one ounce of *compound tincture of* benzoin

PITYRIASIS (TINEA) VERSICOLOR

This is such a common infection in Indians of the poorer classes that they are usually quite unconscious of its existence and are often unable to appreciate the fact that their skin is not normal, even when the lesions are pointed out to them. It has a wide distribution amongst natives in other tropical countries. It is much less common in fair skinned persons, but does occur and it is not strictly confined to hot countries though it is much commoner in them.

Although this infection is widespread in certain social groups, it is *not highly contagious and needs close association before it is transmitted* from one person to another

Ætiology—It is caused by *Malassezia furfur* The fungus invades the superficial layer of the epithelium and causes a fine scaling. There is practically no inflammatory reaction

Symptomatology—The visible lesions are actually accumulations of fungus on the skin where they form yellowish or brownish plaques. On the brown skin they appear as a whitish layer of powder and on the white skin they produce brownish patches As well as the surface lesions there is apparently some change in the underlying pigment, a decrease in the brown skin and an increase in the fair one The lesions commence as small macules the size of a pin's head, they increase in size and coalesce. There is a fine powdery desquamation if the affected area is rubbed.

The distribution of the lesions is very characteristic. It corresponds to an area on to which dandruff would naturally fall from the hair *that is to say* over the shoulders on the front and back of the chest, and on the outer aspects of the arms Sometimes the lesions also appear on the abdomen, neck and face but seldom on other parts of the body These are not the covered areas in the class of individual who usually suffers from this condition as some writers state. The distribution seems to suggest that the hair may be an important source of infection.

Diagnosis.—The condition is readily recognized clinically but confirmation can be obtained easily by taking a scraping from the area, macerating it in potassium hydroxide and examining it under the microscope The grape-like clusters of spores will be seen

Treatment.—This presents little difficulty Most fungicides will destroy this superficially situated fungus very easily *The commonest* application is sodium sulphite 10 to 25 per cent solution. This is washed over the affected area after it has been bathed and well scrubbed Or an ointment containing 3 per cent salicylic acid and 6 per cent precipitated sulphur can be rubbed in The hair should be washed also and the sulphite lotion or some other suitable antiseptic applied to it

The condition will usually clear up within a few days but treatment must be continued for several weeks and all the usual precautions

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* This consists of 10 c.cm of a saturated alcoholic solution of basic fuchsin in 100 c.cm. of 5 per cent phenol in water Filter this and add 1 gramme of boric acid After two hours add 5 c.cm of acetone and two hours later 10 grammes of resorcinol Keep in dark stoppered bottles.

regarding the changing and sterilization of clothes must be taken if relapse and re-infection are to be obviated

LEUCODERMA or VITILIGO

Definition—Leucoderma or vitiligo is an acquired condition in which in certain areas there is complete loss of skin pigment. It is characterized clinically by the appearance of ivory white patches surrounded by an area of normal or increased pigmentation. It is neither infectious nor hereditary, though at times it seems to show a familial tendency.

Epidemiology—It appears to be much more common in tropical countries but it occurs throughout the world in people of all races all ages and both sexes.

Ætiology—The cause of leucoderma is not known. It is usually classed as a tropho-neurosis. In India it has been observed that in the majority of the cases there is some intestinal infection—protozoal bacterial, or helminthic—and it has been suggested on rather slender experimental evidence that the condition may be due to a hyperadrenia, resulting from toxic stimulation of the suprarenals. It has been pointed out that, although kala azar and leucoderma are relatively common in Bengal both conditions are seldom encountered in the same patient. In kala azar there is some evidence of hypoadrenia.

Pathology—Apart from the total absence of pigment the affected skin is not changed in any way the activities of the sweat and sebaceous glands are uninfluenced but the hair shafts in the affected area sometimes lose their pigment and become whitish or yellowish in colour.

Symptomatology—The lesions appear as small white macules and extend slowly. The margins may remain clear-cut but in the larger patches they tend to become less sharply defined. Sometimes there is an increase of pigment in the adjoining areas but there is seldom a definite ring of hyperpigmentation around the leucodermic patches.

In the well-developed case the lesions can be classified into several types (*a*) the muco-cutaneous type affecting the lips eyelids and external genitals (*b*) the pressure type affecting such areas as the waist when there is continuous pressure from clothes the *dhoti* the *sari* or the belt (*c*) the symmetrical type and (*d*) the generalized type where the white patches fuse to form large lobulated areas and even progress so far that the original skin coloration is completely obliterated.

The condition may remain stationary for years but is generally slowly progressive in its course in exceptional instances the patches disappear spontaneously. There are no somatic symptoms associated with this condition but the mental effect of the grotesque disfigurement that may be produced is often profound. The lesions give rise to no subjective symptoms but the whitened patches are hypersensitive to heat and tend to become inflamed readily when exposed to the sun.

Differential diagnosis—The diagnosis does not usually present much difficulty but it is necessary to exclude certain other conditions in which there is complete or partial depigmentation namely (*a*) the congenital condition partial albinism (*b*) the bacillary infection leprosy (*c*) the mycotic infection pityriasis versicolor (*d*) the spirochætal infection (i) pinta (ii) atrophic macular syphilide and possibly (iii) melano-leucoderma (*e*) the protozoal infection post kala azar dermal leishmaniasis and (*f*) conditions of unknown ætiology (i) morphœa and (ii) lupus erythematosus

(*a*) In partial albinism, the lesions are congenital there is never any bordering of the depigmented patch by hyperpigmented skin and the patient always has a blue iris.

(b) In anæsthetic leprosy there may be depigmentation but it is not usually as complete and there are definite sensory changes that are not found in leucoderma there will also be thickened nerves and other stigmata of leprosy. There is little real similarity between these two conditions but there is a popular misconception on the subject due partially to biblical misguidance which reacts very unfavourably on the unfortunate (but non-infectious) individual with leucoderma.

(c) In pityriasis versicolor the depigmentation is mainly due to the whitish mycotic growth on the surface with little hypopigmentation and certainly no true depigmentation there is also slight scaling in the lesions. Laboratory confirmation should be unnecessary but the spores and hyphæ of *Malassezia furfur* can be demonstrated

(d i) In pinta, which has a limited geographical distribution, there is a history of the earlier lesions of this condition, which are characteristic and quite unlike leucoderma there is usually a positive Wassermann reaction, and possibly some slight response to arsphenamine

(d ii) Atrophic macular syphilide is a condition where multiple small atrophic areas are found on the trunk and extremities, and the atrophy is more marked than the depigmentation

(d iii) *Melano-leucoderma* generally affects the palms and the soles and rarely the lips it manifests itself by the appearance of patchy leucoderma and melanoderma (hyperpigmentation) side by side, and also hyperkeratosis with desquamation. The hyperpigmentation is more marked along the margins and sometimes extends higher up to the hands and feet. The disease is probably a late manifestation of syphilis the serum reaction for syphilis is positive in all cases and it responds to anti-syphilitic treatment

(e) In post kala azar dermal leishmaniasis, the depigmentation is not complete. There will nearly always be other lesions, the butterfly erythema on the face or the granulomatous nodules As a rule a history of kala-azar or at least of a febrile attack that may have been kala-azar will be given

(f i) In morphœ, the skin shows different grades of depigmentation with smooth shiny atrophic patches adherent to the underlying tissue.

(f ii) In lupus erythematosus the leucoderma like depigmentation, which is present is due to cicatricial fibrous atrophy of the skin. Apart from the depigmentation the lupus patches are covered by the characteristic fine adherent horny plugs, which when removed reveal enlarged follicular orifices. Moreover the borders of the patches are markedly raised and infiltrated These signs are absent in leucoderma

TREATMENT

This is far from satisfactory and many writers dismiss the condition as incurable However at the Calcutta School of Tropical Medicine over a period of years the routine procedure indicated below has been worked out this appears to give satisfactory results in a small percentage of cases (Panja * 1941 and Panja and Maplestone 1940)

A **General treatment.**—The stools are examined repeatedly for evidence of any intestinal infection amœbic, bacillary or helminthic If such an infection is found the appropriate course of treatment is given. As in addition there is frequently a non specific bowel disturbance suggestive of excessive fermentation half to one drachm of liquor hydrargyri perchloridi (B.P) is given twice daily after meals in courses of three to four weeks with intervals of one to two weeks for a period of at least three to six months

B **Diet**—The patient is advised to avoid food that is likely to cause intestinal fermentation and to take germinating *gram* beans and peas which are rich in vegetable protein and yield a good supply of tyrosin a precursor of melanin.

C **Local treatment**—Oil of bouchi (*Psoralia corylifolia*) is rubbed gently on the lesion twice a day for 5 to 10 minutes each time Sometimes the oil produces intense redness burning and even vesication after a few applications and in susceptible persons the reaction may appear after a

* This useful paper has been quoted freely in this section.



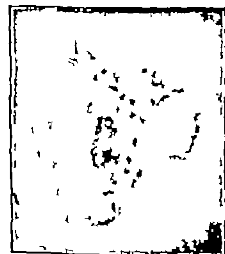
FIG. 1—Tinea imbricata Photograph of a typical case showing concentric rings of scales

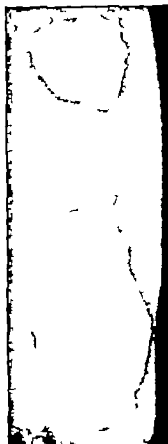


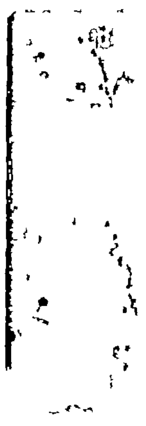
FIG 2.—Tinea imbricata. Photomicrograph of a primary culture from a scale on Sabouraud's medium.



FIG 3—Leucoderma before treatment







SOME RECENT ADVANCES

INTRODUCTION

THE war has affected tropical medicine in a number of ways. In the first place the fact that so many of the theatres of war are in the tropics has made it necessary for a much wider dissemination of knowledge of tropical medicine amongst the personnel and prospective personnel of the armed forces. This, and the danger that many of the fighting men and members of the auxiliary forces will return to their mother countries with infections acquired in the tropics has forced the medical profession in general, and the teaching staffs of medical schools in particular, to take a much livelier interest in tropical medicine and to make some attempt to remedy the defects in their knowledge of tropical diseases.

Secondly, amongst the medical personnel of the armed forces that are being sent into tropical countries there are many physicians and surgeons who are especially skilled in some branch of medicine. Whether or not they are employed in their particular specialties these men will inevitably view tropical diseases from their own particular points of view and bring to bear on these diseases their own special methods of investigation. These studies will not only have a very stimulating effect on the practice of tropical medicine in the tropics but will undoubtedly enrich medical science and bring about a better understanding of the underlying pathological processes; this in turn will lead to the evolvement of better methods of diagnosis, treatment and prevention of tropical diseases. Further, after the war, it is probable that many of these men will maintain their interests and continue their studies in these diseases, and thereby prevent, or at least delay, a return to the pre-war 'isolationist' policy that has had as unfortunate results in the medical as in the political world.

Thirdly, the invasion of tropical areas by large numbers of non-immune white troops will certainly bring to light the wide prevalence of many tropical infections in localities where on account of the relative or absolute immunity to these infections enjoyed by the indigenous populations, they were hitherto unrecognized or at least looked upon as rare.

Fourthly, because of the sensitiveness of these white troops to minor degrees of ill health and because of the careful medical scrutiny to which they are subjected the early signs, symptoms and other evidence of pathological reaction, of many tropical infections will be studied much more thoroughly than was possible hitherto when the majority of cases were among members of the native population who seldom sought medical advice before the disease was well advanced.

Finally, the urgent necessity for improving the methods of prevention and treatment of tropical diseases has led to intensive research work in Britain and America on many aspects of these diseases. Effective vaccines against several infections for which there was no prophylactic hitherto available, many remarkable insecticides and insect repellents and new specifics for several diseases have been prepared.

This is not the ideal moment to report these advances as it will be several years after the war before the results of such work can be

summarized and evaluated It will be a pity if isolated observations how ever carefully made, are incorporated into the textbooks prematurely, that is before they have been shown to be of general application Medical practice amongst the well-disciplined members of the armed forces and under conditions where expense is not a prime factor is very different from practice amongst the highly individualistic and perhaps uneducated and very poor, members of a civil population Further, much of this information is not yet available and much that is available to the privileged is not yet released for general publication

MALARIA

Malaria has again maintained its reputation as the most important tropical disease and in most war zones it has been responsible for many times more deaths and sickness than all other tropical diseases together Further in many areas it has proved a far greater menace than the enemy and perhaps one of the major triumphs of the medical corps in this war has been their achievement in making the combatant officers appreciate this fact and agree to share the responsibility for malaria control.

Malaria control.—It can probably be said that no entirely new principles in malaria control have been evolved but with better tools at their disposal many of which have been discovered during the war remarkable results have been achieved by the medical and sanitary corps of the armed forces and some of the most malarious islands of the South Pacific have been almost entirely freed from malaria

Larva control has been revolutionized by the introduction of DDT This has made it possible for example, to spray effectively from an air plane exhaust an acre of water with as little as 2 ounces of DDT in the form of a 10 per cent powder mixed with talc powdered soapstone or road dust, where it required over a pound of paris green. This has also been used effectively in jungle areas For spraying on water a 1.5 per cent solution of DDT in kerosene or sump oil is many times more effective than the oil alone and lasts several weeks Other similar and even more effective substances have been prepared and are now being used by the army

The freon aerosol spray and the aerosol bomb for personal use were very valuable for *adult mosquito destruction* in huts tents foxholes and trenches even when they depended on pyrethrum for their lethal properties but they became infinitely more deadly when DDT* was added. A well-sprayed wall remains lethal to any insect settling on it for a month or more but for long residual action it is better to use a spray containing 5 per cent DDT in kerosene 1.0 gramme of DDT will make 100 square feet of wall lethal for mosquitoes for 2 to 3 months

Several new repellents including dimethyl phthalate for applying to the uncovered parts of the body have been introduced. Some of these are far more effective than the older repellents and remain active for at least 4 hours but probably the most important advance in this direction has been achieved by the impregnation of the clothing with DDT (25 per cent DDT concentrate in xylene and an emulsifier diluted with 11 parts of water) Clothes thus impregnated maintain their protective qualities for as much as 6 weeks including five or six washings

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* A recent formula is DDT 3 per cent pyrethrum per cent xylohexanone 5 per cent, hydrocarbon oil 5 per cent, and freon 85 per cent

e have been many occasions during this war when mosquito
vas impossible and *drug prophylaxis* was the only practical
Success in drug prophylaxis depends entirely on the complete
tion of all concerned and it was seldom achieved until the res-
ty for enforcing malaria discipline was placed on the com-
g officers of units The dosage is discussed below
nical and pathological studies.—If one overlooks the inevit
discoveries of the protean nature of the clinical manifestations of
a that have been made by those who have not read their textbooks
gently and have expected the standard descriptions of the com
clinical types to cover all cases, the viewing of this disease from
irections by physicians with wide experiences in temperate climate
ad a very healthy effect on the study of malaria Perhaps one o
nost important results has been a fuller realization that the pathol
l picture in most severe cases of malignant tertian malaria is that
k caused by the widespread blocking of capillaries and arterioles l
ky parasitized red cells with the resultant anoxia of the local
ues This concept has led to a reconsideration of the treatment in
cerebral and algid forms of malaria The change has been in two
ections (*a*) a questioning of the advisability of giving intravenous
nine in such cases combined with a tendency now to substitute the
nost equally rapidly acting intramuscular atebrin and (*b*) a freer use
plasma transfusions

Specific treatment—The enormous volume of work on malaria that
as been undertaken in the United States and Britain will almost certainly
ead to greater advances in treatment but as yet no new outstanding drug
as been discovered However the pharmacological investigations have
ed to the adoption of more rational treatment procedures than the empiri-
cal ones that had hitherto been followed and the introduction of better
and more standardized methods of estimating atebrin in the blood and
urine have made these procedures almost indispensable in any well
equipped institution where malaria is treated scientifically The atebrin
blood level necessary to effect a cure was calculated to be about 30
microgrammes per litre This level was attained too slowly with the
atebrin dosage previously adopted but it was shown that it could be
rapidly and safely achieved by the process of loading the dosage during
the first 24 hours The routine course suitable for the oral treatment of
the non immune soldier is 0.2 gramme given immediately and repeated
six hourly night and day up to the end of 24 hours a total of 1 0 gramme
followed by 0 1 gramme thrice daily for six days which brings the grand
total up to 2 8 grammes in a week For parenteral dosage indicated
only when the patient is vomiting unconsciou or has a particularly
heavy *P falciparum* load (50 000 parasites or more per c.mm.), 0.2
gramme is given every six or eight hours up to the same total of 1 0
gramme in the first 24 hours but the oral route is of course the route
of choice and must always be adopted as early as possible This dosage
does not prevent relapses which must be treated as they arise

The unpleasant by effects of atebrin can be to a great extent obviated
or modified by giving a gramme of sodium bicarbonate a spoonful of
glucose or simply a cup of sweet tea with each dose It has also been
shown that tolerance to atebrin is readily achieved and even the rar
psychotic sequelæ will usually not recur if a second course of atebrin has
to be given

There seems little evidence that the extensive lichen planus that has
occurred in groups of soldiers in the South Pacific has any ætiological
connection with the atebrin that many of them were taking

Suppressive drug therapy—drug prophylaxis.—The older regimes (*e.g* 0.2 gramme atebrin twice weekly) were found to be inadequate for the non-immune and larger (than the A iatics on experience with whom previous regimes were mainly based) Australian British and American soldiers It has been found that the necessary blood level to prevent the development of clinical malaria (12 microgrammes) is achieved if 0 1 gramme of atebrin is given daily for two weeks before entry into an endemic area and of course continued for the whole period of residence therein If earlier protection is required this can be achieved by doubling the dose for the first week or giving a loading dose of 0 6 gramme on the first day and continuing with the daily dose of 0.1 gramme this latter will give immediate protection to a very large majority of those taking it. If this suppressive treatment is continued for two weeks after the subject leaves the endemic area complete and permanent protection against *Plasmodium falciparum* infection is achieved but subject infected with *P vivax* or *P malariæ* will in almost every case have an attack of malaria between the third and the sixth week of discontinuing the suppressive drug.

LEISHMANIASIS

Numerous sporadic cases of kala azar have occurred amongst both British and American troops who have been stationed in Bengal and Assam Some of these have escaped detection until they had returned home there are likely to be more such undetected cases

Both acute and insidious onsets have occurred, but on the whole the attacks have been more acute than those usually seen in natives in the endemic area In most instances the disease has been suspected and a parasitological diagnosis made relatively early before the serum-globulin tests the aldehyde the antimony etc have become positive spleen and sternum punctures have been used and most observers have found the former more reliable

Most cases have proved relatively resistant to treatment this was to be expected in view of the fact that the treatment was usually undertaken in the first month or so of the disease Neostibosan was available in the United States and was the drug of choice there but in Great Britain other pentavalent compounds have been used Several drug manufacturers have made a preparation similar to solustibosan (Bayer) and have marketed it under several different names Advantage has been taken of its very low toxicity to give it in much larger doses than those used hitherto and to facilitate this the drug has been issued in lower dilutions *e.g* 25 per cent several experienced workers have reported very good results The diamidines have not lived up to their early promise stilbamidine is the only one that has proved really effective but on account of its toxicity its use has had to be limited to resistant cases

In the prevention of leishmania infections it seems possible that DDT may prove a very important aid. Sandflies seldom fly more than a few feet at a time usually progressing in a series of hops a foot or less in length. This means that before entering a door or window they will nearly always alight on the frame so that spraying or painting with a solution of DDT (*see* above under Malaria) the frames of doors and windows and the walls immediately surrounding them inside and outside should provide an effective barrier against the entry of sandflies More effective control would of course be achieved by treating the whole of the inside wall but this may prove superfluous How far it will be possible to apply this measure in the endemic areas where the majority of the people live in huts with rough walls and roofs and openings around the

SUBJECT INDEX

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